Evaluation of a Cognitive and a Morphometric Marker for the Early Detection of Alzheimer's Disease

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Aging is the accumulation of changes in a person over time

(Bowen & Atwood, 2004)

Contents

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Summary

Alzheimer's disease (AD) is an incurable and devastating neurodegenerative disorder characterized by progressive decline in memory and other cognitive functions ultimately leading to a dementia syndrome when the patient is incapable of independent living. Current treatments provide only temporary symptomatic stabilisation. Improved treatment methods that are now under investigation may be most efficacious in preclinical or early disease stages (Golde, Schneider, & Koo, 2011; Sperling, Jack, & Aisen, 2011), referred to as mild cognitive impairment (MCI). However, some MCI patients develop dementia other than AD, whereas others remain stable or even recover (Roberts et al., 2014). Accordingly, the establishment of markers that accurately identify future converters to AD represents a major contemporary goal in AD research worldwide.

Structural magnetic resonance imaging (MRI) represents a key imaging marker for the early detection of AD. It allows the quantification of brain atrophy due to early involvement of neurofibrillary tangle formation followed by neuronal loss. Although hippocampal atrophy represents a well-established imaging marker for AD, gray matter volume alterations of a single structures may not specifically be associated with AD pathology (van de Pol et al., 2006), and thus might not be sufficient to characterize the spreading pattern of AD pathology across the brain. Taking into account more regional information about volume and shape of further subcortical structures thus might enhance the early detection of AD.

Similarly, impaired episodic memory performance has demonstrated predictive value for conversion from MCI to AD (for an overview see Gainotti, Quaranta, Vita, & Marra, 2014). Nevertheless, the discrimination between impaired cognitive abilities due to low educational background, state-based cognitive fluctuations and AD-related cognitive impairment is challenging (Kliegel & Sliwinski, 2004). Previous studies have demonstrated that considering intraindividual variability (IIV) across accuracy scores (accuracy-based IIV) obtained from tests representing different cognitive domains (across-domain IIV) might increase the prediction of AD (Holtzer, Verghese, Wang, Hall, & Lipton, 2008). Marked IIV is thought to reflect impairment of cognitive control functions, supported by specific regions in prefrontal (Levy & Wagner, 2011; Weissman, Roberts, Visscher, & Woldorff, 2006) and parietal (Wilk, Ezekiel, & Morton, 2012) cortices. However, accuracy-based IIV across tests of cognitive control functions (within-domain IIV) has not been examined in AD. Thus, the aim of the present work was to investigate the value of accuracy-based IIV and shape alterations in subcortical structures as cognitive and morphometric markers for the early detection of AD.

The first study was performed to gain information about two different accuracy-based IIV scores in AD. Specifically, across-domain IIV and within-domain IIV were compared between healthy control subjects (HCS), MCI and AD patients. Both IIV scores were increased in AD when compared with HCS. However, only across-domain IIV was higher in AD than in MCI, and only within-domain IIV

was higher in MCI than in HCS. Thus, results indicate that within-domain IIV in particular might represent a marker for the detection of prodromal AD at the MCI stage, whereas across-domain IIV may detect beginning AD at the MCI stage.

Accordingly, the second study aimed to explore whether within-domain IIV might act as an early marker for AD. For this aim, IIV was investigated in MCI with stable cognitive abilities (MCI-S), MCI with future conversion to AD at baseline (MCI-CB) and HCS. A further aim involved investigating the relationship between within-domain IIV and gray matter volumes of IIV-relevant regions such as dorsolateral and ventrolateral prefrontal as well as posterior parietal cortices (Levy & Wagner, 2011; Weissman et al., 2006; Wilk et al., 2012), obtained by MRI. In contrast to a previous study (Lövdén et al., 2013), within-domain IIV was not associated with regional gray matter volumes in either of the groups. Considering results from studies investigating neuronal correlates of IIV across reaction time tasks (latency-based IIV) (e.g Bunce et al., 2013) and previously reported relationships between latency- and accuracy-based IIV (Hilborn, Strauss, Hultsch, & Hunter, 2009; Hultsch, MacDonald, & Dixon, 2002), within-domain IIV might be associated with white matter rather than with gray matter alterations. More importantly, however, within-domain IIV was not increased in MCI-S nor in MCI-CB or in pooled MCI when compared with HCS. Although the low samples size in this study together with the low characterization of accuracy-based IIV in general (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000) might have triggered this finding, within-domain IIV was found to have questionable value as an early marker of AD.

The third study investigated whether subcortical shape alterations assessed by MRI might support the characterization of future converters to AD. Based on early AD pathology (Braak & Braak, 1990, 1991a) and the pronounced connection of the thalamus and striatum to other AD-relevant structures such as the hippocampus (Zarei et al., 2010), shape alterations in the thalamus and striatum were investigated in MCI-S, MCI-CB and in MCI-CB at time of conversion (MCI-CC). At the same time, established morphometric markers such as cortical thickness and hippocampal total and subfield volumes were investigated. Results demonstrated the simultaneous presence of thalamic and striatal shape alterations, AD-typical mediotemporal cortical thinning and hippocampal atrophy in MCI-CB and MCI-CC but not in MCI-S. These results highlight the value of subcortical shape alterations as an early marker for AD, and emphasize the importance of considering regional morphological information from subcortical structures.

In conclusion, findings from the present work support the value of thalamic and striatal shape alterations to further improve the identification of subjects at high risk for AD whereas within-domain IIV has questionable value as an early marker for AD and needs further exploration. Generally speaking, the present findings further emphasize the key role of morphometric markers for the characterization of early AD stages and indicate a potentially superior role of morphometric over cognitive markers. The value of cognitive markers, particularly when assessed on one single occasion, might be restricted due to limitations inherent to the cognitive tests themselves.

Zusammenfassung

Die Alzheimer-Krankheit (AK) ist eine neurodegenerative Krankheit, welche aufgrund zunehmender kognitiver Beeinträchtigungen zu Demenz und schliesslich zum Verlust der persönlichen Unabhängigkeit führt. Die Wirkung aktuell zugelassener Behandlungsmethoden geht dabei nicht über eine vorübergehende symptomatische Stabilisierung hinaus. Neue Behandlungsmethoden werden aktuell untersucht, wobei Studienresultate darauf hinweisen, dass deren Wirksamkeit in präklinischen oder frühen Krankheitsphasen am höchsten ist (Golde et al., 2011; Sperling, Jack, et al., 2011). Die frühe Krankheitsphase zeichnet sich durch eine leichte kognitive Beeinträchtigung (LKB) aus, wobei nicht alle Patienten mit LKB eine AK entwickeln. Vielmehr gibt es Patienten die andere Demenzformen entwickeln sowie Patienten, deren kognitive Beeinträchtigungen über lange Zeit stabil bleiben oder sich wieder normalisieren (Roberts et al., 2014). Aufgrund dieser Heterogenität stellt die Entwicklung von Markern zur Identifizierung von künftigen AK-Patienten eines der Hauptziele der AK-Forschung weltweit dar.

Die Verwendung struktureller Magnetresonanztomographie (MRT) hat wesentlich zur Identifizierung wichtiger Marker beigetragen. Mittels MRT kann die Atrophie quantifiziert werden, welche sich aufgrund der Bildung von Neurofibrillen und anschliessendem Neuronen Verlust in den Gehirnen von AK-Patienten manifestiert. Obwohl sich insbesondere die Atrophie im Hippocampus als Früherkennungsmarker etabliert hat, muss diese nicht zwangsläufig mit AK in Zusammenhang stehen (van de Pol et al., 2006). Es ist deshalb fraglich, ob die Berücksichtigung von Veränderungen in einer einzelnen Hirnstruktur ausreicht, um die sich im Gehirn ausbreitende AK-Pathologie angemessen zu charakterisieren. Der Miteinbezug weiterer struktureller Veränderungen, insbesondere regionaler Veränderungen subkortikaler Strukturen, könnte entsprechend zur Verbesserung der Früherkennung beitragen.

Neben den MRT-Markern haben auch beeinträchtigte Leistungen im episodischen Gedächtnis einen hohen Vorhersagewert für die Entwicklung einer AK bewiesen (Überblick in Gainotti et al., 2014). Im klinischen Alltag stellt die Unterscheidung kognitiver Beeinträchtigungen aufgrund eines niedrigen Bildungshintergrundes, situationsbedingter kognitiver Fluktuationen oder LKB aufgrund von AK allerdings eine Herausforderung dar (Kliegel & Sliwinski, 2004). Bisherige Studien haben gezeigt, dass die Früherkennung von AK verbessert werden kann, wenn die kognitive intraindividuelle Variabilität (IIV) berücksichtigt wird (Holtzer et al., 2008). Dabei wurde IIV über Trefferquoten in Aufgaben berechnet, welche Leistungen verschiedener kognitiver Domänen erfassten (domänenübergreifende IIV). Erhöhte IIV wurde wiederholt mit beeinträchtigten kognitiven Kontrollfunktionen (West, Murphy, Armilio, Craik, & Stuss, 2002) sowie präfrontalen (Levy & Wagner, 2011; Weissman et al., 2006) und parietalen (Wilk et al., 2012) Hirnregionen in Verbindung gebracht. Dennoch gibt es kaum Studien, die in LKB- oder AK-Patienten IIV über Trefferquoten von Aufgaben untersucht haben, welche verstärkt kognitive Kontrollfunktionen beanspruchen (domänenspezifische IIV). Das Ziel der vorliegenden Arbeit war es deshalb zu untersuchen, ob IIV

über Trefferquoten sowie Formveränderungen in subkortikalen Strukturen als kognitive respektive morphometrische Marker zur Früherkennung von AK beitragen können.

Mit der ersten Studie sollten dabei allgemeine Informationen zu den zwei unterschiedlichen IIV-Werten (domänenübergreifende und domänenspezifische IIV) in AK gewonnen werden. Zu diesem Zweck wurden die beiden IIV-Werte von Patienten mit LKB und AK mit IIV-Werten von gesunden Kontrollpersonen (GKP) verglichen. Dabei stellten sich beide IIV-Werte in AK-Patienten im Vergleich zu GKP als erhöht heraus. Zudem war die domänenübergreifende IIV in AK-Patienten höher als in LKB, während die domänenspezifische IIV bei LKB höher war als in GKP. Damit liefern die Resultate der ersten Studie Hinweise darauf, dass insbesondere die domänenspezifische IIV zur Früherkennung von AK in LKB beitragen könnte.

Diese Annahme wurde mit der zweiten Studie näher untersucht. Zu diesem Zweck wurde die domänenspezifische IIV in LKB mit stabilen kognitiven Fähigkeiten (LKB-S), in LKB mit späterer Entwicklung von AK unter Verwendung des Ausgangswertes (LKB-AKA) und in GKP untersucht. Zudem sollte der Zusammenhang zwischen IIV und dem Volumen der grauen Hirnsubstanz in IIV-relevanten Regionen untersucht werden. Diese wurden mittels strukturellem MRT gemessen und umfassten dorsolaterale und ventrolaterale präfrontale sowie posteriore parietale Rindengebiete (Levy & Wagner, 2011; Weissman et al., 2006; Wilk et al., 2012). Im Gegensatz zu Resultaten einer früheren Studie (Lövdén et al., 2013) wurde dieser Zusammenhang in der vorliegenden Studie in keiner der untersuchten Gruppen gefunden. Diverse Studien haben einen Zusammenhang zwischen IIV über Reaktionszeiten und Veränderungen in der weissen Hirnsubstanz gefunden (z.B. Bunce et al., 2013). Weitere Studien haben zudem gezeigt, dass IIV über Reaktionszeiten und IIV über Trefferquoten korreliert sind (Hilborn et al., 2009; Hultsch et al., 2002). Diese Resultate weisen darauf hin, dass domänenspezifische IIV allenfalls eher mit Veränderungen in der weissen statt mit Veränderungen in der grauen Hirnsubstanz in Zusammenhang stehen könnte. Im Gegensatz zu den Resultaten der ersten Studie hat sich in der zweiten Studie aber vor allem gezeigt, dass domänenspezifische IIV weder in LKB-S noch in LKB-AKA höher war als in GKP. Obwohl es möglich ist, dass die eher kleinen Patientengruppen sowie die generell eher niedrige Ausprägung von IIV über Trefferquoten (Hultsch et al., 2000) zu diesem Resultat geführt haben könnten, ist es dennoch eher fraglich, ob domänenspezifische IIV tatsächlich zur Früherkennung von AK beitragen kann.

Im Rahmen der dritten Studie wurde untersucht, ob Formveränderungen in bestimmten subkortikalen Hirnstrukturen zur Früherkennung von AK beitragen können. Aufgrund ihrer ausgeprägten Verbindungen zu anderen AK-relevanten Strukturen wie dem Hippocampus (Zarei et al., 2010) sowie aufgrund der frühen AK-Pathologie (Braak & Braak, 1990, 1991a) wurden der Thalamus und das Striatum in LKB-S, in LKB-AKA und in LKB-AKA zum Zeitpunkt der AK-Diagnose (LKB-AKD) untersucht. Gleichzeitig wurden bereits etablierte morphometrische Marker wie die kortikale Dicke und die Volumina des Hippocampus und seiner Teilbereiche erhoben und untersucht. Die morphometrischen Veränderungen, die sich in LKB-AKA sowie in LKB-AKD aber nicht in LKB-S zeigten, umfassten nicht nur ausgeprägte Formveränderungen im Thalamus und im Striatum, sondern

auch ein AK-typisches Muster, bestehend aus reduzierter kortikalen Dicke in mediotemporalen Regionen und reduzierten Volumina sowohl im gesamten Hippocampus als auch in den meisten seiner Teilbereiche. Diese Resultate bestätigen den potentiellen Wert morphometrischer Veränderungen in subkortikalen Strukturen für die Früherkennung von AK. Gleichzeitig betonen sie die Wichtigkeit, regionale morphometrische Veränderungen mehrerer subkortikaler Strukturen zu berücksichtigen.

Zusammenfassend weisen die Resultate der vorliegenden Arbeit darauf hin, dass Formveränderungen im Thalamus und im Striatum mögliche morphometrische Marker für die Früherkennung darstellen, während domänenspezifische IIV als kognitiver Marker eher fraglich ist und weiterer Untersuchungen bedarf. Insgesamt liefern die vorliegenden Resultate eine weitere Bestätigung für die Schlüsselrolle morphometrischer Marker in der Früherkennung von AK sowie Hinweise darauf, dass diese den kognitiven Markern überlegen sind. Die Rolle der kognitiven Marker scheint dabei aufgrund testbezogener Eigenschaften limitiert zu sein, insbesondere dann, wenn die Marker anlässlich eines einzigen Messzeitpunktes erhoben werden.

1 Introduction

The world's population is aging and as a direct consequence it is estimated that 44.35 million people worldwide currently live with dementia, reaching 75.62 million in 2030 and 135.46 million in 2050 (Alzheimer's Disease International, 2013). Alzheimer's disease (AD) is the most common cause of dementia and is responsible for 50-70% of dementia cases (Masters, Cappai, Barnham, & Villemagne, 2006). Clinically, AD is an incurable, disabling, and devastating neurodegenerative disorder characterized by progressive decline in memory and other cognitive functions ultimately leading to a dementia syndrome when the patient is incapable of independent living. Current treatments provide only symptomatic relief for a short period. Improved treatment methods that are now under investigation may be most efficacious in preclinical or early disease stages (Golde et al., 2011; Sperling, Jack, et al., 2011), referred to as mild cognitive impairment (MCI). However, the development of cognitive and clinical symptoms varies even in MCI. Some subjects develop dementia other than AD, whereas others remain stable for a long time or even recover (Roberts et al., 2014). Accordingly, the establishment of markers that accurately identify individuals at risk for AD represents a major contemporary goal in AD disease research worldwide.

Structural magnetic resonance imaging (MRI) represents a key imaging marker for the early detection of AD, with hippocampal atrophy in particular being present at the earliest stages of AD (Jack et al., 2013; Johnson, Fox, Sperling, & Klunk, 2012). However, gray matter volume alterations of a single structure may not necessarily be associated with AD pathology (van de Pol et al., 2006), and thus, might not be sufficient to characterize the progression of AD pathology across the brain. Reports of early AD pathology in other subcortical structures (Braak & Braak, 1990, 1991a, 1991b; Braak & Del Tredici, 2011) have indicated that the early detection of AD might be improved when more regional information about shape of further subcortical structures is taken into account.

Likewise, episodic memory impairment represents a well-established cognitive marker for the early detection of AD (for an overview see Gainotti et al., 2014). However, despite extensive evidence for the advantageous use of cognitive markers, the reliable detection of early cognitive impairment based on mean cognitive performance in clinical routine still poses a challenge. In particular, the discrimination between impaired performance due to low educational background, daily fluctuations and AD-related cognitive impairment (Kliegel & Sliwinski, 2004), or the detection of subtle cognitive changes in general (Drago et al., 2011) complicate the identification of AD-related cognitive alterations.

Both cognitive and structural markers can easily be obtained by applying non-invasive methods. Clinical standard MRI and neuropsychological assessments are widely available in clinical settings, represent financially favorable methods and pose only minimal burden to the patient. Thus, the present work aims to extend the knowledge about cognitive and structural measures by investigating the potential value of a newly developed cognitive marker and of alterations in subcortical structures as early markers for AD. After the introduction in chapter 1, chapter 2 will provide background

information about disease-related pathology, criteria for the diagnosis of AD and MCI, biomarkers for AD in general, and cognitive and morphometric markers in particular. The methods section in chapter 3 will then provide information about the participants, cognitive and morphometric variables and applied techniques. Chapter 4 will outline the aims and research questions, followed by the empirical studies in chapter 5. Chapter 6 will discuss and summarize the results and will comment on implications and future directions.

2 Theoretical background

2.1 Alzheimer's disease pathology

Amyloid-β (Aβ) peptides (Glenner & Wong, 1984; Masters et al., 1985) and hyper-phosphorylated tau protein (Mandelkow, Von Bergen, Biernat, & Mandelkow, 2007) represent the main components of extracellular amyloid plaques and intracellular neurofibrillary tangles (NFT), both representing major histopathological hallmarks of AD (Jellinger, 1990). In the predominant amyloid cascade hypothesis, Aβ in particular has been assumed to represent the trigger for AD (Hardy & Selkoe, 2002). More precisely, it has been suggested that the discrepancy between production and decomposition of Aβ might result in the production of plaque, and eventually of NFT, followed by neuronal dysfunction, degeneration and clinical symptoms (Hardy, 2009).

Concurrently, NFT has moved increasingly into focus as a potentially responsible trigger of AD pathology. Specifically, it has been assumed that abnormally phosphorylated tau (p-tau) impairs axonal transports and leads to intraneuronal aggregation of NFT, synaptic dysfunction, and neuronal loss (Walker, Diamond, Duff, & Hyman, 2013). Moreover, the pattern of NFT formation has been suggested to better reflect AD-typical atrophy patterns. Thus, and similar to atrophy patterns (Tondelli et al., 2012; Whitwell et al., 2012), early NFT has been identified in perirhinal and entorhinal cortices with further extension to hippocampal and other mediotemporal regions, followed by the involvement of neocortical association areas of the temporal, parietal and frontal lobes (Braak & Braak, 1991b). Primary sensory areas, however, have been found to be involved only in later disease stages (Braak & Braak, 1995). Outside the cerebral cortex, the earliest and most severe NFT has been identified in anterior thalamic regions (Braak & Braak, 1991a, 1991b) with the striatum being spared until later disease stages (Braak & Braak, 1990, 1991b). In contrast, Aβ depositions have been shown to follow a different pattern, with early depositions in the basal frontal, temporal and occipital lobe and subsequent expansion to the striatum and cholinergic nuclei of the basal forebrain (Braak & Braak, 1991b; Thal, Rüb, Orantes, & Braak, 2002). Thalamic subnuclei have been involved later and less severely (Braak & Braak, 1991a, 1991b), followed by cerebellar Aβ deposition, and with hippocampal regions being only mildly involved for a long time (Braak & Braak, 1991b). Accordingly, it has been assumed that Aβ aggregation represents an early and necessary, though not sufficient, pathological feature leading to cognitive impairment in AD (Reitz, 2012).

Although the role of Aβ and tau, and the exact mechanisms that trigger and promote neurodegeneration in the brain remain to be fully understood, Aβ- and tau-related measures are still in the focus of AD researchers in the quest for markers for the early detection of AD. Consequently, their presence increases the likelihood of AD diagnosis in the current diagnostic recommendations for probable AD.

2.2 Diagnostic criteria for Alzheimer's disease

The criteria for the diagnosis of probable AD were established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) in 1984 (McKhann et al.). Mainly due to advances in methods allowing for the reliable detection of Aβ and tau, NINCDS-ADRDA criteria were reviewed in 2011. Briefly, the current criteria for the diagnosis of probable AD (McKhann et al., 2011) require the presence of a decline in cognitive or behavioral functioning involving at least two of five domains (memory, executive functions, visuospatial abilities, language, personality), significantly interfering with the patient's ability to perform activities of daily living. Furthermore, insidious symptom onset as well as early and most pronounced deficits in memory and in at least one other cognitive domain must be met. Clinically significant cerebrovascular disease, features of other forms of dementia, or any other active comorbidity that might have caused cognitive worsening must be absent. Evidence of a disease-relevant genetic mutation further increases the certainty of AD diagnosis. Markers showing amyloid deposition in the brain (positron emission tomography [PET] amyloid imaging) or reduced Aβ in cerebrospinal fluid (CSF) (lumbar puncture), or neurodegeneration indicated by reduced glucose metabolism (^{18}F-Fluordesoxyglucose [FDG]-PET), increased gray matter atrophy (structural MRI) or increased tau in CSF further increase the confidence of AD-related pathology accounting for the dementia syndrome. It has to be noted, however, that the application of these pathological markers for diagnostic purposes in the current criteria were mainly considered for research but not clinical use. This was for methodological reasons such as limited availability of some of the involved methods and the lack of standardizations and cut-off values at that time (McKhann et al., 2011).

2.3 Early detection of Alzheimer's disease

2.3.1 Mild cognitive impairment

MCI refers to the transitional zone between normal aging and AD (Petersen, 1995). Although memory deficits represent the hallmark of MCI, cognitive impairments in general must not be sufficient to affect activities of daily living (Petersen, 2004; Petersen et al., 2001; Winblad et al., 2004). Results from longitudinal studies have shown an increased risk for MCI patients to develop dementia within a few years (Gallagher et al., 2010; Petersen, 2004), and MCI has therefore been recognized as a risk state for dementia (Gauthier et al., 2006). Four different subtypes have been distinguished (Petersen, 2004; Petersen et al., 2001; Winblad et al., 2004): isolated memory impairment (amnestic single domain, aMCIs), impairment in memory and other cognitive domains (amnestic multiple domain, aMCIm), impairment in a single non-memory domain (non-amnestic single domain, nMCIs) or

impairment in more than one non-memory domain (non-amnestic multiple domain, nMCIm). Of the proposed subtypes, amnestic MCI (aMCI) in general, and aMCIm in particular have demonstrated a higher probability of progressing to AD (e.g. Roberts et al., 2014). In contrast, non-amnestic subtypes have been identified as prodromal states for non-AD dementias (Bäckman, Jones, Berger, Laukka, & Small, 2005; Mitchell & Shiri-Feshki, 2009).

Nevertheless, there has been heterogeneity with regard to the longitudinal development of cognitive abilities and other clinical symptoms. The annual conversion rates from aMCI to AD vary from 4% to 20% (Dickerson, Sperling, Hyman, Albert, & Blacker, 2007; Landau et al., 2010; Maioli et al., 2007; Mitchell & Shiri-Feshki, 2009; Rabin et al., 2009; Schmand, Eikelenboom, & van Gool, 2012; Tabert et al., 2006), with lower rates in population-based samples, and higher rates in clinical samples. Accordingly, there is a considerable proportion of aMCI whose cognitive abilities remain stable over long periods of time (Fisk, Merry, & Rockwood, 2003; Mitchell & Shiri-Feshki, 2009; Roberts et al., 2014) or even recover (Forlenza et al., 2009; Roberts et al., 2014). When compared to healthy control subjects (HCS), the risk for conversion to AD has recently been found to be higher in MCI who had reverted back to normal cognitive abilities at least once (Roberts et al., 2014). Less is known about the long-term development of cognitive functions in MCI with stable cognitive abilities. Some authors have referred to this stage as a potential early stage of AD (Bossa, Zacur, & Olmos, 2011) whereas others have just referred to a long-lasting diagnostic stability (Bakkour, Morris, & Dickerson, 2009; Li et al., 2012; Tang et al., 2014). These results emphasize the heterogeneous long-term development of cognitive abilities in MCI, complicating the identification of future converter subjects.

2.3.1.1 Diagnostic criteria for Mild cognitive impairment

The current criteria provide recommendations not only for MCI due to AD (Albert et al., 2011), but also for preclinical AD (Sperling, Aisen, et al., 2011). Preclinical AD is diagnosed in the presence of Aβ deposition and/or neurodegeneration and the simultaneous absence of clinical symptoms such as memory impairment. In contrast, MCI due to AD is diagnosed in the presence of cognitive decline, evidence of impairment in one or more cognitive domains but preserved functional abilities and no dementia diagnosis. Although there is no differentiation between subtypes, it has been noted that memory impairment is commonly present in future converters (Albert et al., 2011). If information about AD pathology is available, MCI due to AD are additionally required to reveal either a positive biomarker reflecting Aβ deposition or neurodegeneration. If one biomarker is positive, there is an intermediate likelihood of future conversion to dementia whereas the likelihood is high for subjects with both biomarkers being positive. MCI is unlikely to be due to AD if both biomarkers are negative. Nevertheless, and for similar reasons as described in section 2.2, the use of AD markers has mainly been proposed for research settings.

Importantly, by establishing the presence of AD pathology already in preclinical stages of AD, the current incorporation of AD markers emphasizes the suggestion that AD pathology represents a continuum (Sperling & Johnson, 2013).

2.3.2 Biomarker

Biomarkers are biological factors that can be measured and represent the presence or absence of pathophysiological processes (Alzheimer's Association, 2014). In the case of AD, pathophysiological processes involving Aβ and tau have been shown to be present 20 years or more before clinical symptoms occur (Jack et al., 2009; Reiman et al., 2012; Villemagne et al., 2013). Thus, biomarkers play a crucial role in the early detection and diagnosis of AD. Acknowledging this fact, the five most widely studied biomarkers of AD have been incorporated into the current diagnostic criteria (Albert et al., 2011; McKhann et al., 2011; Sperling, Aisen, et al., 2011). Moreover, these biomarkers have been integrated into a hypothetical model (Jack et al., 2013) that assumes that AD biomarkers become abnormal in a temporally ordered way (Jack et al., 2009; Mormino et al., 2009; Perrin, Fagan, & Holtzman, 2009). The model, therefore, provides useful information for improving the early detection of AD.

In particular, and referring to previous research, the model assumes that markers of Aβ accumulation become abnormal first, with CSF Aβ becoming atypical slightly before amyloid PET imaging. Markers of neurodegeneration become abnormal later, with CSF tau levels becoming atypical first (e.g. Braak, Zetterberg, Del Tredici, & Blennow, 2013; Buchhave et al., 2012), followed by MRI and FDG-PET. However, based on results from autopsy studies (Braak & Del Tredici, 2011), the model also proposes that tau pathophysiology might appear in subcortical regions very early, with Aβ pathophysiology starting later and independently (Jack et al., 2013). Initial subcortical tauopathy, however, can only be detected by using immunostaining methods but may accelerate the preceding subcortical tauopathy (Musiek & Holtzman, 2012; Price & Morris, 1999). The model furthermore assumes a strong relationship between neurodegenerative markers and cognitive performance in MCI and AD (Jack et al., 2000; Vemuri et al., 2010) but a weak relationship between Aβ markers and cognitive performance (Jack et al., 2008; Jack et al., 2009; Lim et al., 2013). Importantly, the model has also posits that factors such as age, genetics, and education in particular are most likely responsible for differences in the time lag between beginning Aβ accumulation and the onset of clinical symptoms.

This model has gained a lot of attention, and since then, many biomarker studies have been performed to further evaluate the biomarkers themselves and the model's assumptions. However, several drawbacks to these AD biomarkers need to be considered. As mentioned in previous sections, there is a lack of well validated and accepted normative and cut off values for most biomarkers (Sperling & Johnson, 2013). With regard to CSF measures in particular, high variation between centers due to variations in assays pose a challenge (Forlenza, Diniz, Teixeira, Stella, & Gattaz, 2013). Furthermore, the collection of CSF by lumbar puncture remains invasive and has been associated with health risks. With respect to amyloid PET imaging, it remains unknown whether there is a threshold or cut off value at which the tracer uptake represents a pathological signal (Sperling, Aisen, et al., 2011). Furthermore, the presence of amyloid deposition in the brain does not necessarily establish AD as this

has also been found in other neurodegenerative diseases such as Lewy body dementia (Mulugeta et al., 2011) or frontotemporal dementia (Perneczky et al., 2011), but also in HCS (Villemagne et al., 2011). Importantly, the clinical applicability of amyloid PET imaging is reduced due to limited registration as a diagnostic tool, high costs, and the application of radioactive tracers posing a burden to the patient.

Consequently, more work is needed to establish reliable thresholds and cut offs for well-known biomarkers on the one hand, and to investigate the potential of further biomarkers that can be implemented in clinical settings on the other hand.

2.3.3 Morphometric markers

According to the previously introduced biomarker model from Jack et al. (2013), structural MRI markers represent rather late occurring biomarkers. Nevertheless, structural MRI has become a key imaging marker for the early detection of AD, and the comparison of regional brain volumes across groups of HCS, MCI and AD represents the most established approach in AD research. Brain atrophy has been associated with NFT (Yushkevich et al., 2014) and cognitive impairment (Ferrarini et al., 2014), and its regional pattern has been shown to correspond with the pattern of progressing NFT in AD (see section 2.1). Here, a short overview of the most established structural MRI markers for AD will be provided. Given the relevance of gray matter alterations in AD, the focus will be on measures providing global or regional information about changes in gray matter structures (hereafter referred to as morphometric measures). Subsequently, a recently developed marker that might further support the early detection of AD will be introduced.

2.3.3.1 Established morphometric markers

So far, most researchers have focused on measuring mediotemporal atrophy. Atrophy of the hippocampus and entorhinal cortex in particular has been demonstrated early in the AD disease course (e.g. Tapiola et al., 2008; Tondelli et al., 2012). Hippocampal shrinking represents the key imaging marker for AD (Cummings, Dubois, Molinuevo, & Scheltens, 2013) and has been incorporated in the current research criteria for MCI (Sperling, Aisen, et al., 2011) and AD (Albert et al., 2011). Results from histology studies have indicated that hippocampal subfields are affected differently by neurofibrillary tangle formation, with the earliest and most prominent involvement of cornu ammonis (CA)1 followed by the subiculum, and later involvement of CA2 and CA3 (Braak & Braak, 1991b; Braak, Braak, & Bohl, 1993; Rossler, Zarski, Bohl, & Ohm, 2002). Corresponding atrophy patterns have recently been found in MCI (Apostolova, Dinov, et al., 2006; Atienza et al., 2011; La Joie et al., 2013; Pluta, Yushkevich, Das, & Wolk, 2012; Yushkevich et al., 2014) and AD (Apostolova, Dinov, et al., 2006; Frankó, Joly, & the Alzheimer's Disease Neuroimaging Initiative, 2013; Frisoni et al., 2008; Li, Dong, Xie, & Zhang, 2013). Local analysis of the structure, therefore, has been viewed as advantageous for the early detection of dementia (Maruszak & Thuret, 2014; Tang et al., 2014).

Volumes of other subcortical nuclei have received less attention, and results about volume reductions in AD have been mixed. Atrophy in the amygdala, putamen, caudate, and thalamus have indeed been identified in AD (Cho et al., 2014; de Jong et al., 2014; Stepan-Buksakowska et al., 2014; Tang et al., 2014). Others, however, could not identify comparable atrophy in AD (Cho et al., 2014; Stepan-Buksakowska et al., 2014). Importantly, similarly mixed results have been reported with regard to subcortical atrophy in MCI (Bossa et al., 2011; Leh et al., 2014; Tang et al., 2014; Zhang et al., 2013).

Cortical thickness analysis has been suggested to represent a more sophisticated way to measure brain atrophy (Lerch & Evans, 2005) and thus constitutes another widely accepted approach to assess gray matter atrophy in AD. Specifically, cortical thinning has been found in patients with MCI and AD (Lerch, Pruessner, et al., 2008; Liao et al., 2014), in future converters when compared to healthy controls (Liao et al., 2014), and to predict conversion to AD in MCI (Querbes et al., 2009). Typically, AD-associated cortical thinning has been identified in temporal and medial temporal, lateral parietal and frontal cortices, as well as in the limbic system (Bakkour et al., 2009; Dickerson et al., 2009; Lerch, Pruessner, et al., 2008; Li et al., 2012; Liao et al., 2014; Peters, Villeneuve, & Belleville, 2014; Ye et al., 2014).

Although gray matter alterations assessed by MRI represent valuable biomarkers for AD, hippocampal atrophy in particular has shown only moderate specificity as it has also been seen in normal aging (Apostolova et al., 2012), in hippocampal sclerosis (Dawe, Bennett, Schneider, & Arfanakis, 2011) and in other forms of dementia (de Souza et al., 2013; La Joie et al., 2013; Tondelli et al., 2012). Moreover, by taking into account the progressing pattern of AD pathology across the brain (see section 2.1), the appropriate characterization of AD might require the consideration of multiple structures. Additionally, as results from hippocampal subfield analyses have indicated, more local information about different structures might further contribute to the characterization of AD-typical patterns of morphometric alterations.

2.3.3.2 Subcortical alterations

The thalamus and the striatum in particular represent structures that might be of high value for the early detection of AD for many reasons. More precisely, the thalamus consists of different subnuclei, with anterior subnuclei in particular being affected by AD pathology very early (Braak & Braak, 1991a, 1991b). Furthermore, the structure is highly connected with other AD-relevant structures such as the hippocampus (Zarei et al., 2010) and has been linked with memory, attention, visuospatial perception, and emotion processing (Arend, Henik, & Okon-Singer, 2014; de Bourbon-Teles et al., 2014; Saalmann, 2014; Wilke, Kagan, & Andersen, 2013), and hence, with AD-related cognitive impairment. The neostriatum consisting of the putamen and caudate nucleus (hereafter referred to as striatum) in turn has revealed NFT at rather late histopathological disease stages (Beach et al., 2012; Braak & Braak, 1990, 1991b; Thal et al., 2002). Similar to the thalamus, however, the striatum has

been linked to a wide range of cognitive functions such as attention, planning and memory (Cummings, 1995), all representing functions that are impaired early in AD (Klekociuk, Summers, Vickers, & Summers, 2014). The possibility of early AD-related alterations in these structures is therefore highly likely. Due to improvements in segmentation and analysis techniques, recent results have indeed provided evidence for alterations in the thalamus (Roh et al., 2011; Stepan-Buksakowska et al., 2014; Zarei et al., 2010), putamen (Cho et al., 2014; de Jong et al., 2014; Roh et al., 2011), and caudate nucleus (Cho et al., 2014; Madsen et al., 2010; Roh et al., 2011) in AD. However, less is known about subcortical volumetric and shape differences in MCI in general, and in future converters in particular.

2.3.4 Cognitive markers

A large number of studies have evidenced a long period and slow rate of cognitive decline that may occur up to a decade before MCI or AD have been diagnosed (e.g. Amieva et al., 2014), with a period of more rapid deterioration and more pronounced deficits several years before the clinical onset of MCI (Howieson et al., 2008). Thus, cognitive markers have demonstrated the potential as early markers for AD.

2.3.4.1 Established cognitive markers

Impaired memory functions including deficits in episodic and semantic memory functions represent cognitive hallmarks of AD that have repeatedly been found in healthy elderly subjects who later developed dementia, as well as in MCI and in AD patients (for an overview see Gainotti et al., 2014). Delayed recall deficits in particular have reliably predicted conversion to AD in MCI.

Similarly, deficits in executive functions have been well documented in both MCI and AD patients (e.g. da Costa Armentano, Porto, Nitrini, & Dozzi Brucki, 2013), and have been shown to predict conversion to AD in healthy elderly subjects (Wilson, Leurgans, Boyle, & Bennett, 2011). Furthermore, corresponding declines have been found up to three years before AD onset (Grober et al., 2008). In particular, performances on tasks assessing working memory (Amieva et al., 2004; Brandt et al., 2009; Wilson et al., 2012), task switching (Chen et al., 2000; da Costa Armentano et al., 2013; Dickerson et al., 2007), inhibitory control (Amieva et al., 1998; Rainville et al., 2002), cognitive flexibility and cognitive control (Rapp & Reischies, 2005; Schroeter et al., 2012) as well as problem solving and planning (Brandt et al., 2009; da Costa Armentano et al., 2013) have represented early clinical signs.

Deficits in other cognitive domains such as language, attention and visuospatial functions have also been reported in MCI (Belleville, Chertkow, & Gauthier, 2007; McLaughlin, Anderson, Rich, Chertkow, & Murtha, 2014; Taler & Phillips, 2008), with more pronounced deficits in AD (Chen et

al., 2001; Tsantali, Economidis, & Tsolaki, 2013; Vasquez et al., 2011). However, their consideration is mainly of high importance for the identification of MCI not due to AD, with prominent attentional, visuospatial or language deficits representing hallmarks for Lewy body dementia (McKeith et al., 2005), posterior cortical atrophy (Mendez, Ghajarania, & Perryman, 2002) and primary progressive aphasia (Gorno-Tempini et al., 2011), respectively.

These encouraging results, however, conceal the fact that the reliable detection of early cognitive impairment in clinical routine still poses a challenge. The lack of a standard use of cognitive tests, and of tests that allow the valid and reliable assessment of particular cognitive functions or even subtle cognitive alterations in, for example, highly educated subjects hamper the identification of early cognitive impairment. Additionally, there is no uniformly accepted cut-off for the definition of cognitive impairment. Therefore, there is a need to identify cognitive markers that enable the detection of the earliest cognitive alterations even in the absence of objective impairment on standardized testing.

2.3.4.2 Intraindividual variability in cognitive performance

Intraindividual variability (IIV) in cognitive performance has been found to represent a potentially more sensitive early marker of cognitive impairment (Dixon et al., 2007; MacDonald, Hultsch, & Dixon, 2008), and might overcome some of the above-mentioned limitations that have been associated with standardized testing. IIV has been recognized as a stable trait reflecting central nervous system pathology (Hultsch et al., 2000) and can be defined as behavioral changes that may occur quickly and over relatively short time frames (Nesselroade, 1991). IIV across multiple trials of a single reaction time task or across different reaction time tasks assessed on one occasion (latency-based IIV) have been shown to be increased in MCI (Christensen et al., 2005; Dixon et al., 2007; Duchek et al., 2009; McLaughlin, Borrie, & Murtha, 2010; Phillips, Rogers, Haworth, Bayer, & Tales, 2013; Strauss, Bielak, Bunce, Hunter, & Hultsch, 2007) and AD (Hultsch et al., 2000; Jackson, Balota, Duchek, & Head, 2012; Phillips et al., 2013; Rochat et al., 2013). The implementation of latency-based IIV measures in clinical routine, however, is complicated by the requirement to integrate repeatedly applied reaction time tasks in already comprehensive neuropsychological test batteries. Additional and repeatedly applied tests might further increase the burden for these already stressed patients.

IIV computed across the accuracy scores (accuracy-based IIV) obtained from different widely established cognitive tests has, therefore, offered an alternative approach. Although accuracy-based IIV has not been investigated extensively in AD, results have been promising for predicting incident dementia (Holtzer et al., 2008) and probable AD (Vaughan et al., 2013).

With regard to neural correlates, IIV has been proposed to index neurobiological disturbance (Hultsch, Strauss, Hunter, & MacDonald, 2008) and failure to maintain cognitive control (West et al., 2002). Cognitive control processes and IIV are thought to be supported by dorsolateral and ventrolateral prefrontal cortices (dlPFC; vlPFC) (Levy & Wagner, 2011; Liston et al., 2006) and parietal cortex

regions (PCC) (Wilk et al., 2012). Only a few studies have examined structural correlates of accuracy-based IIV in general, but results provide support for an association between reduced prefrontal gray matter volume and higher IIV in healthy older adults (Lövdén et al., 2013).

3 Methods

3.1 Participants

The studies included in the present work were performed by merging the baseline and follow-up data of elderly subjects that were enrolled in three different and still on-going longitudinal as well as one cross-sectional study located at the Memory Clinic at the Division of Psychiatry Research and Psychogeriatric Medicine, University of Zurich. The primary aim of all studies was to identify risk factors for dementia.

Briefly, participants were recruited from the outpatient population of the Memory Clinic or through advertisements in the local media. HCS were additionally recruited through inquiries of caregivers or relatives of the patients. All diagnoses were made by a multidisciplinary team under the supervision of an experienced psychiatrist and according to Winblad criteria for MCI (Winblad et al., 2004), and NINCDS-ADRDA criteria for AD (McKhann et al., 2011). Details about inclusion and exclusion criteria will be provided in the empirical part (chapter 5).

Visits of the longitudinal studies were scheduled every 12 to 18 months. MCI subjects classified as critical for conversion to dementia received additional 6 months screenings. Baseline and follow up visits of the longitudinal studies included: screenings for depression including Hamilton Rating Scale for Depression (Hamilton, 1960) or Hospital Anxiety and Depression Scale-Deutsche Version (HADS-D) (Herrmann-Lingen, Buss, & Snaith, 2011), screening for cognitive functioning Clinical Dementia Rating Scale (CDR) (Morris, 1993), cognitive disorder Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), comorbidity Cumulative Illness Rating Scale (CIRS) (Salvi et al., 2008), and Instrumental Activities of Daily Living (IADL) (Lawton & Brody, 1969) as well as psychiatric, neurological and internal diseases, and other disorders that could potentially produce cognitive impairment. MRI data were assessed in two of the studies, and scans were performed at baseline and follow up visits. Amyloid-PET imaging with the 11(C)-Pittsburgh compound B was performed in one study at baseline and at three year follow up visits.

All studies were approved by the cantonal ethics committee of canton Zurich, Switzerland. Subjects were only included after providing written informed consent. Details about the identification of subsamples relevant for the present work will be provided in the empirical part (chapter 5).

3.2 Neuropsychology

The neuropsychological test battery was administered at baseline and follow up visits. Apart from the CERAD-plus test battery (Thalmann et al., 1997), the following tests were applied to evaluate five cognitive domains: Verbaler Lern- und Merkfähigkeitstest (VLMT) (Helmstaedter, Lendt, & Lux,

2001), nonverbal and verbal Paired Associates test (Wechsler Memory Scale-Revised [WMS-R]) (Härting et al., 2000), and recall of the Rey-Osterrieth Complex Figure (ROCF) (Meyers & Meyers, 1995) for verbal and nonverbal memory functions; category and letter fluency (Aschenbrenner, Tucha, & Lange, 2000), Five-Point Test (Regard, Strauss, & Knapp, 1982), Stroop interference score (Troyer, Leach, & Strauss, 2006), Trail Making Test (TMT) ratio B/A (Reitan, 1958), Visual and Verbal Memory Span backward (WMS-R) (Härting et al., 2000) for executive functions; TMT A and B (Reitan, 1958), Visual and Verbal Memory Span forward (WMS-R) (Härting et al., 2000) for attention and psychomotor speed; Boston Naming Test (BNT) (Thalmann et al., 1997) for language abilities; Clock Drawing Test (Rouleau, Salmon, Butters, Kennedy, & McGuire, 1992) and copy of the ROCF for visuo-constructive and visuo-spatial abilities. Impairment was defined if at least one score per domain was 1.5 standard deviations (SD) below group means provided by test-specific normative data.

3.3 Intraindividual variability

Based on the few but promising results obtained from studies examining accuracy-based IIV in AD research (see section 2.3.4.2), the potential value of two different accuracy-based IIV scores as early markers for AD was examined. On the one hand, based on other studies (Brewster, Tuokko, & MacDonald, 2012; MacDonald, Brewster, Laukka, Fratiglioni, & Bäckman, 2012; Tractenberg & Pietrzak, 2011), IIV was calculated across accuracy scores obtained from cognitive tests assessing different cognitive domains each (across-domain IIV). On the other hand, based on the assumption of a close relationship between IIV and cognitive control processes supported by the frontal cortex (MacDonald, Li, & Bäckman, 2009), IIV was calculated across accuracy scores obtained from three tests, each eliciting recruitment of cognitive control processes (within-domain IIV). Further details about the identification of relevant tasks will be provided in the empirical part (chapter 5).

IIV can be computed in different ways. The simplest method is to compute the mean intraindividual standard deviation (ISD) across each individual's standardized performance scores (Slifkin & Newell, 1998), with higher standard deviations indicating higher IIV. A disadvantage of ISD, however, is its dependence on the mean (Nesselroade & Salthouse, 2004). In particular, increased IIV in reaction time tasks may reflect increased mean performance and thus, poorer performance (Hale, Myerson, Smith, & Poon, 1988) whereas in non-speeded tasks, increased IIV may be associated with higher performance (Allaire & Marsiske, 2005). Accordingly, this may result in increased accuracy-based IIV in HCS due to their higher mean performance. Mean performance and ISD may furthermore be artificially correlated due to floor and ceiling effects, with extreme performers showing smaller IIV (Baird, Le, & Lucas, 2006). Thus, individual mean performances represent a potential confounder and need to be considered when examining IIV scores. In the context of the present work, each individual's mean performance was considered as a covariate in all relevant analyses. More detailed information about the calculation of IIV will be provided in the empirical part (chapter 5, study 1 and 2).

3.4 Structural magnetic resonance imaging

A full description of the complex physical principles on which structural MRI is based is beyond the scope of this work. Briefly, the imaging of brain structures is based on the magnetic characteristic of hydrogen atoms in the human brain as well as the radio frequency signal and its decay after having been exposed to the static magnetic field of the scanner and temporarily applied radio frequency electromagnetic pulses (Weishaupt, Köchli, & Marincek, 2006). Different tissue types can then be distinguished based on different magnetization properties. Due to its high contrast, T1 weighted data in particular allows the differentiation of gray matter, white matter and CSF.

The manual delineation of human neuroanatomical structures on T1 weighted data still represents the gold standard for the identification of brain structures. The enormous time investment as well as high inter- and intra-rater variability (Chakravarty, Sadikot, Germann, Bertrand, & Collins, 2008; Chakravarty et al., 2009), however, represent substantial drawbacks and have supported the development of fully automated segmentation methods. The present work involves well-known, sophisticated, and fully automated methods for the assessment of established AD biomarkers such as hippocampal and hippocampal subfield volumes as well as cortical thickness. Furthermore, in order to investigate alterations in subcortical structures as potential early markers for AD, recently developed and fully automated methods were used to assess the volume and shape of the thalamus and striatum.

For all of the subsequently described analyses, three-dimensional (3D) T1-weighted structural data obtained from a 1.5 Tesla scanner was converted into MINC before being used as input. The conversion to MINC was performed by using the RMINC toolkit (R for Medical Imaging NetCDF; https://github.com/Mouse-Imaging-Centre/RMINC), an image analysis software library developed for the R statistical environment (http://www.r-project.org).

3.4.1 Subcortical segmentation

The recently developed MAGeT (Multiple Automatically Generated Templates) Brain algorithm (Chakravarty et al., 2013) was used for the segmentation of the striatum, the thalamus and its subnuclei as well as the hippocampus and its subfields.

MAGeT Brain is a multi-atlas based segmentation approach that extends standard atlas-based segmentations by automatically generating multiple templates within the dataset of interest from a minimal number of manually labelled brains. This has the added benefit of growing, through automated processes, the number of candidate segmentations available for any single subject. The method has shown improved segmentation of subcortical structures over standard atlas-based segmentation techniques. More precisely, increased segmentation accuracy is achieved by distributing random errors due to anatomical differences, registration, and resampling across the template library. Importantly, MAGeT has demonstrated reliability when compared with manual delineations of the

striatum and the thalamus (Chakravarty et al., 2013). With respect to the hippocampus and its subfields, MAGeT Brain has recently shown reliability in the identification of the subfields based on T1-weighted images obtained from a 1.5 Tesla system, and that it performs comparably, if not better than other established methods (Pipitone et al., 2014).

For the segmentation of the striatum and the thalamus, MAGeT uses a single atlas derived from a set of 84 serial histological and manually segmented slices (Chakravarty, Bertrand, Hodge, Sadikot, & Collins, 2006). The atlas contains definitions for 108 anatomical regions including basal ganglia and thalamic structures (Gloor, 1997; Hirai & Jones, 1989; Schaltenbrand & Wahren, 1977). Segmentation of the hippocampus and its subfields is based on five high-resolution atlases previously developed and validated for use with MAGeT Brain (Pipitone et al., 2014; Winterburn et al., 2013).

Briefly, MAGeT Brain first uses a regular atlas-based segmentation procedure to create a template library, which customizes the above-mentioned atlases to a subset of subjects that are distributed with respect to age, sex and disease category. To this end, the algorithm uses a region-of-interest based nonlinear transformation scheme (Chakravarty et al., 2008; Chakravarty et al., 2009) to match each input atlas to each subject in the template library. As previously demonstrated (Chakravarty et al., 2013; Park et al., 2014; Pipitone et al., 2014), the use of 21 templates is optimal to account for neuroanatomical variability within the sample, and averaging of possible random errors. The newly segmented set of subjects now acts as a template library. As a second step, MAGeT generates multiple segmentations for each subject from the newly developed template library by using estimates of all pairwise nonlinear transformations. Here, the number of candidate segmentations per subject equals: number of atlases used x number of subjects in the template library (21). Lastly, MAGeT applies a voting procedure over all candidate segmentations (Collins & Pruessner, 2010), where the most frequently occurring label at each voxel is kept for the final segmentation output.

3.4.2 Surface-based shape analysis

Shape analysis allows for three-dimensional quantification of inward (contractions) and outward (expansions) movements on the surface, and therefore provides additional and more localized information regarding the previously segmented structures. Since the surface-based methodology used here is still under development, measures for the hippocampus are not available at the current time. In the present work, shape analyses of the thalamus and the striatum was performed using an adapted surface-based methodology, as in previous studies (Lerch, Carroll, et al., 2008; Magon et al., 2014; Raznahan et al., 2014; Shaw, Sharp, et al., 2014).

First, surface-based representations of the segmented structures are created on the input atlas and estimated using the marching cubes algorithm (Lerch, Carroll, et al., 2008). Second, the 21 nonlinear portions of the transformations that map each subject to the input atlas are combined and then averaged across the template library. This procedure has the benefit of reducing the effects of noise and error, and of increasing precision and accuracy (Dorr, Lerch, Spring, Kabani, & Henkelman, 2008;

Frey et al., 2011). Third, global linear effects not originally accounted for in the initial linear transformations are further modeled and removed. This ensures that the contributions of overall differences in brain volume are minimized (Lerch, Carroll, et al., 2008; Raznahan et al., 2014). Fourth, the dot product between the nonlinear deformation vector (of the inverse of the averaged atlas-to-subject transformation) and the surface normal at each vertex (a unit vector describing the direction perpendicular to the surface) is calculated. This measure provides an estimate of the local measure of contractions or expansions along the normal (Lerch, Carroll, et al., 2008). Fifth, surface area values are blurred with a 5mm surface-based diffusion smoothing kernel (Chung et al., 2003). All contractions and expansions, measured in millimeters, are then computed using the structures as defined in the subcortical atlas (Chakravarty et al., 2006) as a reference.

3.4.3 Cortical thickness and cortical gray matter volumes

Cortical thickness measures the thickness of the cortical band encompassing the layers of gray matter. More precisely, the border between gray matter and CSF (gray matter surface) and the border between white matter and gray matter (white matter surface) represent the outer and inner surfaces, and cortical thickness is measured as the distance in millimeters between these surfaces. Different fully automated approaches have been developed (e.g. MacDonald, Kabani, Avis, & Evans, 2000), with varying degrees of precision in terms of defining corresponding points on the two surfaces (Lerch & Evans, 2005).

For the present analyses, the CIVET pipeline (version 1.1.10; Montreal Neurological Institute at McGill University, Montreal, Quebec, Canada) (Ad-Dab'bagh et al., 2006) was used to estimate cortical thickness as well as gray matter volumes of predefined cortical regions. For measuring cortical thickness, CIVET uses deformable models to construct the inner and outer surfaces of the cortex in both hemispheres (Kim et al., 2005). Briefly, the surface deformation algorithm first fits the white matter surface and is then expanded towards the gray matter surface. Thus, white matter vertices are closely linked to their complements of the gray matter surface, and cortical thickness is then measured as the distance between the two surfaces at these linked vertices (Lerch & Evans, 2005). When compared to other methods, this definition of cortical thickness has been suggested to be the simplest and most precise, and to increase statistical sensitivity (Lerch & Evans, 2005). Further detail about particular preprocessing steps for both cortical volumes and cortical thickness will be provided in the empirical part (chapter 5, study 2 and 3).

3.4.4 Intracranial volume

The comparison of gray matter volumes across groups requires taking into account interindividual variability in brain morphology. Values of intracranial volume (ICV) indicate premorbid brain

volume, and thus are often used to adjust volumes for subsequent volume analyses. ICV has been shown to be larger in males than in females, to be only minimally affected by age (Buckner et al., 2004), and to be positively correlated with gray matter volumes of cortical and subcortical brain structures (Barnes et al., 2010; Voevodskaya et al., 2014). When examining volume reductions in neurodegenerative disease, considering ICV allows for estimation of atrophy caused by neurodegenerative mechanisms rather than by interindividual differences in head size and brain morphology.

In the present work, the FreeSurfer pipeline (version 5.1.0) was used to calculate total intracranial volume (eTIV) representing an estimate for ICV as described in Buckner et al. (2004). Briefly, each individual is registered to an atlas template (Talairach & Tournoux, 1988). The Atlas Scaling Factor obtained by this transformation represents the whole-brain volume adjustment that is required to match each individual to the atlas template and is thus used to automatically generate eTIV. This automated method has been shown to be equivalent to manual correction (Buckner et al., 2004) and has previously been used for normalization in several AD studies (Westman, Aguilar, Muehlboeck, & Simmons, 2013; Westman, Muehlboeck, & Simmons, 2012; Westman et al., 2011).

There is no consensus about whether eTIV should be taken into account by using residuals from linear regression between raw volume and eTIV to predict adjusted volumes (Jack et al., 1998), by using eTIV as a covariate in regression models, or by using volumes relative to eTIV (for a discussion see Voevodskaya et al., 2014). In the present work, volume analyses of cortical and subcortical structures (chapter 5, study 2 and study 3) were performed by using raw volumes. However, all analyses were repeated using raw volumes relative to eTIV (volume / eTIV * 100) as described in previous studies examining atrophy-related volume reductions (Goto et al., 2014; Kooistra et al., 2013).

4 Aims and research questions

The primary goal of the present work was to examine the potential of within-domain IIV as well as thalamic and striatal shape alterations as cognitive and morphometric markers for the early detection of AD.

Study 1 - Aims and research questions

The aim was to obtain more information about accuracy-based IIV in AD in general, and about within-domain IIV in particular. This was achieved by the comparison of across- and within-domain IIV scores between HCS and MCI as well as AD patients, and by comparing IIV scores with each other. Additionally, since the APOE ε4 allele represents a risk factor for late-onset AD (Corder et al., 1993; Petersen, 1995), the relationship between IIV and APOE genotype was explored. In particular, the following predictions were made:

Based on results from previous studies (MacDonald et al., 2012; Tractenberg & Pietrzak, 2011), across-domain IIV was expected to be higher in MCI and AD than in HCS.

Based on the suggested relationship between cognitive control functions and IIV (MacDonald et al., 2009) and on impaired cognitive control functions in AD (Rapp & Reischies, 2005; Schroeter et al., 2012), within-domain IIV was also expected to be higher in MCI and AD than in HCS.

Due to the novelty of within-domain IIV, no predictions were made regarding its comparison with across-domain IIV. Assuming that impaired cognitive control functions affect performances in different cognitive control tests to a similar extent, within-domain IIV might indeed be expected to be low. In contrast, tasks underlying across- domain IIV represent distinct cognitive functions that are most likely affected differently. Thus, IIV across these tasks might be higher than within-domain IIV. At the same time, however, impaired cognitive control functions might lead to highly variable performances across tasks in general, and across cognitive control tasks in particular. Thus, within-domain IIV might as well be similar or even higher than across-domain IIV.

Additionally, within-domain IIV in particular was expected to be higher in APOE ε4 allele carriers within each group. This prediction was based on the fact that the frontal lobe has not only been associated with cognitive control (Levy & Wagner, 2011; Liston et al., 2006) and IIV (MacDonald et al., 2009), but also constitutes the brain region that manifests APOE ε4 effects in early disease stages (Filbey, Chen, Sunderland, & Cohen, 2010).

Study 2 - Aims and research questions

The aim was to obtain more information about the structural correlate of within-domain IIV in AD, and about the value of within-domain IIV for early detection. This study, therefore, investigated the

relationship between within-domain IIV and gray matter volumes of IIV-relevant cortical brain regions in HCS, MCI with stable cognitive abilities (MCI-S) and MCI with future worsening of cognitive function and conversion to AD (MCI-CB). Additionally, the ability of within-domain IIV to predict diagnostic group membership was examined. The following predictions were made:

Based on previously reported relationships between structural alterations in prefrontal cortex regions and IIV (Anstey et al., 2007; Jackson et al., 2012; Lövdén et al., 2013), a negative relationship between within-domain IIV and gray matter volumes of dlPFC, vlPFC and PPC was expected in MCI-CB but not in MCI-S.

Based on previous reports about the predictive ability of across-domain IIV (Holtzer et al., 2008) and the assumption that within-domain IIV represents a potentially more sensitive marker for early AD, within-domain IIV was expected to significantly contribute to the prediction of MCI-CB but not MCI-S group membership.

Study 3 - Aims and research questions

The aim was to gain information about the potential value of thalamic and striatal shape alterations to facilitate the identification of future converters to AD. Thus, shape alterations were compared between HCS and MCI-S, MCI-CB and MCI-CB at time of conversion (MCI-CC). Additionally, established analyses techniques were used to further confirm AD-typical hippocampal atrophy and cortical thinning. The following predictions were made:

AD-related neurodegenerative processes, and thus, morphometric alterations were expected in MCI-CB with more pronounced alterations in MCI-CC. In contrast, MCI-S were expected to show only minimal or no alterations at all.

Based on the pattern of NFT formation (Braak & Braak, 1990, 1991a, 1991b) and on results from previous studies (Cho et al., 2014; Ferrarini et al., 2014; Stepan-Buksakowska et al., 2014; Wisse, Biessels, Heringa, et al., 2014), volume reductions in the hippocampus, thalamus and striatum as well as in particular hippocampal subfields (CA1, subiculum) and thalamic (anterior) subnuclei were expected in MCI-CB and MCI-CC.

Further confirming AD related atrophy and the literature (Liao et al., 2014), cortical thinning in mediotemporal as well as lateral cortical regions was expected in MCI-CB and MCI-CC.

Although the neuronal basis of shape alterations is yet unknown, thalamic and striatal shape alterations were expected in MCI-CB and MCI-CC. On the one hand, the assumed volume reductions might lead to shape alterations. On the other hand, the connection with other structures showing early NFT such as the hippocampus (Zarei et al., 2010) might lead to secondary downstream effects and thus, shape alterations in the thalamus and striatum.

5 Empirical part

5.1 Study 1: Intraindividual variability in mild cognitive impairment and Alzheimer's disease patients

Intraindividual variability across cognitive tasks as a potential marker for prodromal Alzheimer's disease

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5.1.1 Abstract

Recent studies have shown that increased cognitive intraindividual variability (IIV) across accuracy scores from tests representing different cognitive domains (across-domain IIV) might indicate prodromal Alzheimer's disease (AD). Although IIV has been proposed to index cognitive control processes, IIV across accuracy scores from cognitive control tasks (within-domain IIV) has not been examined in healthy controls subjects (HCS), mild cognitive impairment (MCI) and AD patients in a single comparative study. This study examines the discriminative properties of within-domain IIV, and across-domain IIV in 149 HCS, 31 MCI and 26 AD. Three tasks representing different cognitive domains were identified to calculate across-domain IIV. Three other tasks representing cognitive control were identified to calculate within-domain IIV. The intraindividual standard deviation (ISD) was calculated across accuracy scores. To compare IIV between groups, ANCOVAs with the covariates age, gender, education, and mean performance were computed. IIV scores in general were higher in AD vs. HCS ($p<0.01$). Only across-domain IIV was higher in AD vs. MCI ($p=0.001$), and only within-domain IIV was higher in MCI vs. HCS ($p=0.05$). Within-domain IIV may constitute a cognitive marker for the detection of prodromal AD at the MCI stage, whereas across-domain IIV may detect beginning AD at the MCI stage.

5.1.2 Introduction

The importance of reliable methods for the early detection of Alzheimer's disease (AD) has increased with the expected availability of treatment methods, which may be most efficacious in preclinical (Masdeu, Kreisl, & Berman, 2012) or early disease stages (Doraiswamy et al., 2002). Cognitive intraindividual variability (IIV) has evidenced representing a potential marker of early cognitive impairment (MacDonald et al., 2009), with IIV across multiple trials of a reaction time (RT) task or across different RT tasks (latency-based IIV) predicting global decline (Hultsch et al., 2002; Lövden, Shu-Chen, Yee Lee, & Lindenberger, 2007) and being increased in mild cognitive impairment (MCI) (Duchek et al., 2009; McLaughlin et al., 2010) and AD (Hultsch et al., 2000; Jackson et al., 2012). However, integrating repetitive RT tasks into already existing comprehensive test batteries may increase the testing-associated burden on patients.

Considering IIV across accuracy scores of different cognitive tasks (accuracy-based IIV) may provide an alternative. Although latency- and accuracy-based IIV have reportedly been associated (Hilborn et al., 2009; Hultsch et al., 2002), the latter has not been studied extensively. However, the use of accuracy-based IIV across tests representing different cognitive domains (across-domain IIV) appears promising for predicting global (Kliegel & Sliwinski, 2004) and functional decline (Morgan, Woods, & Grant, 2012), incident dementia (Holtzer et al., 2008), and probable AD (Brewster et al., 2012). Likewise, it was found to be increased in MCI and AD (MacDonald et al., 2012; Tractenberg & Pietrzak, 2011). Although IIV has been proposed to index cognitive control processes supported by the frontal cortex (MacDonald et al., 2009), accuracy-based IIV across tests representing cognitive control functions (within-domain IIV) to our knowledge has not been examined in healthy control subjects (HCS), MCI, and AD in a single comparative study. Consequently, the aim of our study was to investigate within- and across-domain IIV as markers for prodromal AD. We compared IIV between groups and hypothesized increased levels in MCI and AD. Additionally, and since the APOE ε4 allele represents a risk factor for late-onset AD (Corder et al., 1993; Petersen, 1995; Tang et al., 1996), we explored the relationship between IIV and APOE genotype.

5.1.3 Methods

Study population

A total of 267 subjects (HCS n=180, MCI n=44, AD n=26) from on-going studies at the Memory Clinic of the Division of Psychiatry Research and Psychogeriatric Medicine, University of Zurich, were considered for cross-sectional baseline analysis. Participants were recruited from the outpatient population of the Memory Clinic or by advertisement in the local media. All subjects had complete cognitive baseline data acquired between January 2006 and May 2012.

MCI was diagnosed according to Winblad et al. (2004). Probable AD was diagnosed following criteria from National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984). All diagnoses were made by a multidisciplinary team under the supervision of an experienced psychiatrist. HCS were required to be cognitively healthy and report cognitive well-being. MCI and AD subjects were excluded from the present analyses if there was evidence for the use of psychoactive medication, abuse of alcohol and drugs, other past or present psychiatric or neurological diseases or significant other systemic diseases, or structural abnormalities in the brain assessed by magnetic resonance imaging (MRI) that could account for the cognitive decline. Additionally, HCS were excluded if there was significant medical disease, clinically significant depression or any medication use potentially affecting cognition. Visits included screenings for depression, psychiatric, neurological and internal diseases, and other disorders that could potentially produce cognitive impairment. The neuropsychological test battery consisted of multiple tests covering the following cognitive domains: episodic memory, executive function, attention/psychomotor processing speed, language and visual-constructive abilities. Impairment was defined if at least one score per domain was 1.5 standard deviations (SD) below group means provided by test-specific normative data.

From the original HCS sample, 31 subjects were excluded from the analyses due to clinically significant neurological disease (n=3), alcohol abuse (n=1), medication (n=25), and due to dropout after the assessment (n=2). Due to a change in test batteries, 13 MCI subjects were missing a test score relevant for computing IIV and were excluded from the analyses. Thus, a total of 149 HCS, 31 MCI patients and 26 patients with probable AD were eligible for the current analysis of IIV. The final demographic details are presented in Table 1. This study was approved by the cantonal ethics committee of canton Zurich, Switzerland, in accordance with the Helsinki Declaration. All participants and/or their legal representatives provided written informed consent prior to study inclusion.

Computation of intraindividual variability

Considering the clinical applicability of the IIV scores, we retrospectively identified tasks with less than 1% missing values per diagnostic group. Additionally, we only selected tasks with no ceiling or floor effects to prevent suppressing variation at the extreme ends of the distribution.

For calculating across-domain IIV, we used accuracy scores from three tests, each representing a different cognitive domain: Digit Span Forward from the Wechsler Memory Scale-Revised (Härting et al., 2000) assessing verbal short-term memory capacity (Lezak, Howieson, & Loring, 2004), Word List Learning and Category Fluency from the CERAD-plus test battery (Thalmann et al., 1997) assessing verbal learning and executive function / semantic knowledge, respectively. For calculating within-domain IIV, we used accuracy scores from three tests, each representing executive functions and eliciting recruitment of cognitive control processes. The Letter Fluency test requires participants to name as many words as possible within 3 minutes while taking into account particular restrictions (i.e. no names, geographically related words, labels, repetitions). Participants need to generate, maintain and monitor a plan, to select and establish specific responses and, therefore, access cognitive control (Reiman, Weaver, & Arrington, 2014; Stein, Luppa, Brähler, König, & Riedel-Heller, 2010). Compared with the Category Fluency test, which consists of a single restriction (name animals) and is of a shorter duration (1 minute), the Letter Fluency test represents a more complex task. Increasing task complexity is thought to place higher demands on higher order cognitive abilities (Halford, Baker, McCredden, & Bain, 2005) such as cognitive control processes. Accordingly, the Letter Fluency test is thought to rely more on cognitive control processes but less on semantic knowledge than the Category Fluency task (Delis & Kaplan, 2001). Trial 3 from the Stroop Test (Troyer et al., 2006) requires subjects to accurately name the color in which 24 non-congruent color words are printed (i.e. the word blue is printed in red color). Accordingly, participants need to maintain a goal while inhibiting a routine response in favor of a less familiar one, a process which typically involves cognitive control (West et al., 2002). The Five-Point Test (Regard et al., 1982) represents figural fluency and requires participants to draw as many different figures as possible within 3 minutes by connecting dots displaying the five-dot arrangement on dice. Participants, therefore, need to follow a mental strategy and monitor their performance. This coordination of information to select appropriate behavioral responses represents aspects of cognitive control (Kelemen & Fenton, 2010).

The simplest method to compute IIV is to calculate the intraindividual standard deviation (ISD) (Nesselroade & Salthouse, 2004) across each individual's accuracy scores. Before computing ISD, two missing Stroop Test raw scores in HCS and MCI were imputed with the expected-maximization algorithm in SPSS. Effects associated with age, education and gender, and potential interactions were estimated from the HCS' raw scores by using General Linear Model. Parameters for age, education and gender from this model were used to predict accuracy scores in both MCI and AD subjects. Standardized residuals for MCI and AD were then calculated by subtracting the predicted from the observed accuracy scores and dividing it by the model's standard error. Residuals from the Stroop Test were log-transformed to achieve normal distribution, and multiplied by -1 to adjust for scaling difference. In sum, this procedure generated standardized residuals representing adjusted accuracy scores with a mean of 0 and variance of ~1 in HCS. By restricting the variance to ~1 in HCS, we lowered the risk of overestimating IIV in HCS due to higher mean performance, since ISD is not independent from the mean (Allaire & Marsiske, 2005). Accordingly, residuals deviating from 0 represented adjusted accuracy scores for MCI and AD subjects. We then computed ISD across each individual's residuals on Digit Span Forward, Word List Learning, and Category Fluency representing

across-domain IIV, whereas ISD across residuals on Letter Fluency, Stroop Test, and Five-Point Test represented within-domain IIV. To further address the association between ISD and mean performance, we used the intraindividual mean (IIM) across residuals underlying across-domain IIV (across-domain IIM) and across residuals underlying within-domain IIV (within-domain IIM) as covariates in all relevant analyses.

Genotyping

APOE genotyping was performed by restriction isotyping as described previously (Hixson & Vernier, 1990). For analysis, participants were classified as either carriers (APOE ε2/ε4, ε3/ε4 and ε4/ε4) or non-carriers of the APOE ε4 allele.

Statistics

Group comparisons of normally distributed demographic data, raw and adjusted cognitive data were applied using univariate analysis of variance (ANOVA) followed by Sidak post hoc tests correcting for multiple comparisons. Kruskal-Wallis tests followed by Mann-Whitney tests corrected for multiple comparisons were performed to compare not normally distributed variables. Pearson's chi-square test was used for categorical variables. Univariate analyses of covariance (ANCOVA) with diagnostic group treated as the main effect were performed to evaluate group wise differences in across- and within-domain IIV. Although influences of age, gender and education had already been taken into account while computing IIV, they were used as covariates to control for influences on IIV. Across- and within-domain IIM represented additional covariates. Sum of Square Type III was applied to take into account the unbalanced design. Significant group effects were further examined using Sidak post hoc test correcting for multiple comparisons. For parametric analyses, tests were performed with a significance level of $p < 0.05$. Manually correcting for multiple comparisons, a significance level of $p < 0.017$ ($0.05/3 = 0.017$) was applied for non-parametric analyses. All analyses were performed as two-sided tests by using the statistical analysis software package PASW 19.0 for Windows.

5.1.4 Results

Descriptive statistics for demographic information and adjusted cognitive data, as well as cognitive raw data is listed in Table 1.

Table 1 Demographic information and cognitive measures per diagnostic group

Characteristic		HCS		MCI		AD		*p* Value
N		149		31		26		N/A
Age, y		68.93	5.75	73.39	5.93	77.65	6.10	0.000* [a,b,c]
Gender, M/F[d]		59/90		11/20		7/19		0.455
Years of education		14.51	3.25	12.94	2.95	11.12	2.81	0.000* [a,b]
MMSE[e]		29.43	0.82	27.87	1.77	21.46	3.78	0.000* [a,b,c]
Digit Span Forward	raw	7.49	1.78	5.90	1.33	5.35	1.81	N/A
	res	0.00	0.99	-0.63	0.71	-0.65	1.16	0.000* [a,b]
Word List Learning	raw	23.70	2.87	17.13	4.49	12.27	4.01	N/A
	res[e]	0.00	0.99	-2.25	1.58	-3.91	1.43	0.000* [a,b,c]
Category Fluency	raw	23.91	4.74	17.71	5.10	11.08	5.25	N/A
	res	0.00	0.99	-1.22	1.08	-2.53	1.15	0.000* [a,b,c]
Letter Fluency	raw	31.65	8.93	22.58	10.21	13.23	5.96	N/A
	res	0.00	0.99	0.29	1.52	-0.66	1.12	0.004* [a,c]
Stroop Trial 3	raw	28.36	8.70	35.29	9.94	69.04	48.33	N/A
	res[e]	0.00	0.99	-0.74	1.01	-2.74	2.20	0.000* [a,b,c]
Five-Point Test	raw	25.96	7.00	18.74	6.70	12.19	5.27	N/A
	res	0.00	0.99	-0.91	0.87	-1.70	0.78	0.000* [a,b,c]
Across-domain IIM		0.00	0.63	-1.37	0.82	-2.36	0.92	0.000* [a,b,c]
Within-domain IIM		0.00	0.73	-0.45	0.86	-1.70	0.99	0.000* [a,b,c]
Across-domain IIV[f]		0.91	0.62	0.98	0.58	1.52	0.75	0.001* [a,c]
Within-domain IIV[f]		0.75	0.55	1.01	0.52	1.23	0.65	0.002* [a,b]

Note. HCS = healthy control subjects; MCI = mild cognitive impairment; AD = Alzheimer's disease; N/A = not applicable; MMSE = Mini-Mental State Examination; res = standardized residuals; raw = raw scores; IIM = intraindividual mean; IIV = intraindividual variability. Data are means and standard deviations unless specified otherwise. Standardized residuals of cognitive test scores for MCI and AD were calculated by using parameter estimates for age, education and gender in HCS. * Significant global *p* value test by analysis of variance unless specified otherwise. Post hoc tests indicated significant differences at $p \leq 0.05$ or lower (parametric tests) and $p < 0.01$ or lower (non-parametric tests) for [a]HCS vs. AD; [b]HCS vs. MCI; [c]MCI vs. AD. [d]Pearson's χ^2 test. [e]Kruskal-Wallis test followed by Mann-Whitney test. [f]Analyses of covariance, means adjusted for age, gender, education and across- or within-domain IIM.

Across-domain IIV was influenced by age ($F(1,199) = 3.958$; $p = .048$; $\eta^2_P = .020$), and slightly by across-domain IIM ($F(1,199) = 3.520$; $p = .062$; $\eta^2_P = .017$) but not by education ($F(1,199) = 0.076$; $p = .783$; $\eta^2_P = .000$) or gender ($F(1,199) = 1.346$; $p = .247$; $\eta^2_P = .007$). But first and foremost we observed a main effect between the diagnostic groups ($F(2,199) = 7.310$; $p = .001$; $\eta^2_P = .068$). Patients with AD revealed higher IIV than HCS ($p = 0.002$; 95% CI = 0.192 – 1.030) and MCI ($p = 0.001$; 95% CI = 0.170 – 0.892), whereas IIV did not differ between MCI and HCS ($p = 0.896$; 95% CI = -0.226 – 0.387) (Figure 1, A). Within-domain IIV was not influenced by age ($F(1,199) = 0.054$; $p = .816$; $\eta^2_P = .000$), education ($F(1,199) = 2.237$; $p = .136$; $\eta^2_P = .011$), gender ($F(1,199) = 2.613$; $p = .108$; $\eta^2_P = .013$) or within-domain IIM ($F(1,199) = 1.500$; $p = .222$; $\eta^2_P = .007$), but differed among diagnostic groups ($F(2,199) = 6.330$; $p = .002$; $\eta^2_P = .060$). IIV was higher in AD than HCS ($p = 0.004$; 95% CI = 0.126 – 0.825). But contrary to across-domain IIV, within-domain IIV was similar in AD and MCI ($p = 0.374$; 95% CI = 0.142 – 0.582). More importantly, there was a strong trend for higher IIV in MCI than in HCS ($p = 0.055$; 95% CI = -0.004 – 0.514) (Figure 1, B).

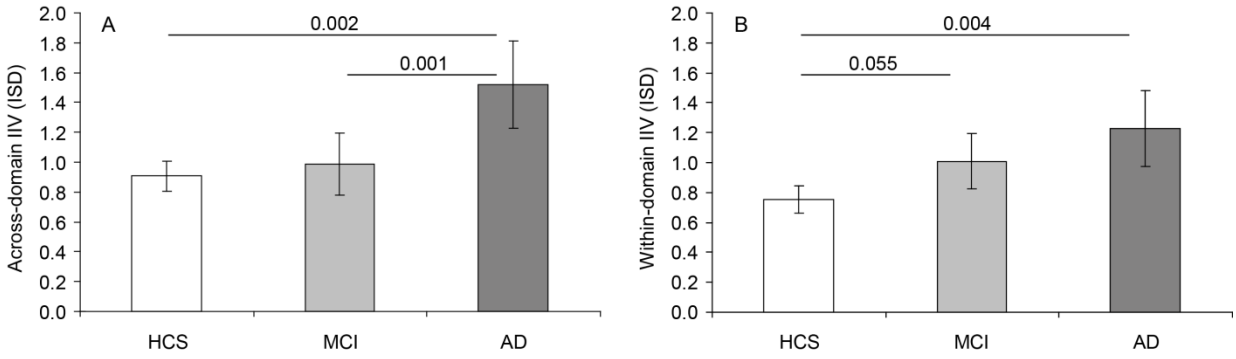

Figure 1 Comparison of intraindividual variability (IIV) scores between diagnostic groups. Intraindividual standard deviation (ISD) representing mean across-domain IIV (**A**) and mean within-domain IIV (**B**) per diagnostic group (HCS = healthy control subjects; MCI = mild cognitive impairment; AD = Alzheimer's disease). Error bars display 95% confidence interval for the mean. Pairwise *p* values shown are based on Sidak Post Hoc tests following analyses of covariance for the omparison of means adjusted for age, years of education, gender, as well as mean across-domain performance (**A**) and mean within-domain performance (**B**) respectively.

To evaluate whether there was a relationship between IIV scores, a difference score was calculated by subtracting within- from across-domain IIV. ANCOVA was performed by treating age, education, gender, and across- and within-domain IIM as covariates. The effect of diagnostic group did not approach significance ($F(2,198) = 1.497$; $p = .226$; $\eta^2_P = .015$), indicating similar differences between IIV scores across diagnostic groups. The qualitative analysis of difference scores, however revealed positive difference scores within each group (HCS: $M = 0.141$, $SD = 0.805$; MCI: $M = 0.005$, $SD =$

0.757, AD: M = 0.340, SD = 0.989), indicating a tendency toward higher across- than within-domain IIV in these groups.

The relationship between APOE status and IIV was explored in a subsample with available genotype. Descriptive statistics for demographic information and adjusted cognitive data is listed in Table 2.

To compare IIV scores between ε4 carriers and non-carriers within each group, we performed ANCOVAs by treating gender as a covariate in MCI. Across-domain IIV did not vary with APOE status in HCS (F(1,111) = 0.368; p = .545; η^2_P = .003), MCI (F(1,27) = 0.227; p = .638; η^2_P = .008) or AD (F(1,21) = 0.003; p = .957; η^2_P = .000). Likewise, within-domain IIV did not vary as a function of APOE status in MCI (F(1,27) = 0.348; p = .560; η^2_P = .013) or AD (F(1,21) = 0.149; p = .703; η^2_P = .007). In HCS, however, there was a weak though significant effect of APOE status (F(1,111) = 3.972; p = .049; η^2_P = .035) indicating increased within-domain IIV in ε4 carriers.

Table 2 Demographic information and cognitive measures per diagnostic group and APOE genotype

Characteristic	HCS				MCI				AD				*p* Value
APOE status	ε4+		ε4-		ε4+		ε4-		ε4+		ε4-		N/A
N[c]	26		87		16		14		9		14		0.004*
Age, y	71.04	5.92	68.89	5.72	73.31	6.44	73.36	5.75	77.33	3.87	78.07	7.43	--
Gender, M/F[d]	11/15		39/48		2/14		9/5		4/5		3/11		0.003*[a]
Years of education	14.77	2.89	14.72	3.52	12.44	2.78	13.57	3.23	10.67	2.18	10.93	3.17	--
MMSE	29.23	0.91	29.47	0.83	27.44	1.50	28.21	1.97	20.56	3.40	21.86	4.11	--
Digit Span forward	0.02	1.14	-0.008	1.03	-0.61	0.67	-0.58	0.74	-0.37	1.34	-0.57	0.99	--
Word List Learning	-0.06	0.94	0.05	1.07	-2.23	1.61	-2.14	1.58	-3.78	1.68	-3.99	1.47	--
Category Fluency	0.33	0.99	-0.06	1.01	-1.37	0.94	-0.89	1.11	-2.39	1.42	-2.63	1.04	--
Letter Fluency	0.57	1.16	-0.11	0.88	0.65	1.13	-0.17	1.83	-1.29	1.33	-0.39	0.88	0.002*[b]
Stroop Trial 3	0.02	0.94	0.07	1.04	-0.94	0.86	-0.44	1.12	-2.78	2.01	-2.95	2.45	--
Five-Point Test	0.25	1.00	-0.05	0.97	-1.03	0.61	-0.77	1.12	-1.71	0.97	-1.77	0.75	--
Across-domain IIM	0.09	0.61	0.00	0.68	-1.41	0.80	-1.20	0.77	-2.18	1.26	-2.39	0.77	--
Within-domain IIM	0.28	0.72	-0.02	0.72	-0.44	0.64	-0.46	1.12	-1.93	1.01	-1.70	1.00	--
Across-domain IIV[e]	0.91	0.46	0.84	0.44	1.03	0.81	1.18	0.22	1.86	0.59	1.84	0.87	--
Within-domain IIV[e]	0.86	0.40	0.68	0.41	0.97	0.47	1.08	0.05	1.33	0.72	1.51	1.22	0.049*[b]

Note. HCS = healthy control subjects; MCI = mild cognitive impairment; AD = Alzheimer's disease; ε4+ = ε4 carrier; ε4- = ε4 non-carrier; N/A = not applicable; MMSE = Mini-Mental State Examination; IIM = intraindividual mean; IIV = intraindividual variability. Data are means and standard deviations unless specified otherwise. Standardized residuals of cognitive test scores for MCI and AD were calculated by using parameter estimates for age, education and gender in HCS. * If not stated otherwise: Significant *p* value test by analysis of variance per diagnostic group indicated significant differences at $p < 0.05$ or lower between ε4 carrier and ε4 non-carrier in [a]MCI, [b]HCS. -- indicate no significant group differences. [c]Pearson's χ^2 test across diagnostic groups. [d]Pearson's χ^2 test per diagnostic group. [e]Analysis of covariance in MCI, means adjusted for gender.

5.1.5 Discussion

This study examined whether two different accuracy-based IIV measures on established neuropsychological tasks differed between HCS, MCI and AD. Our results suggest an increasing breakdown of cognitive control functions early in prodromal AD resulting in increased IIV. More precisely, across- and within-domain IIV, as used in the present study, may differ from each other as a function of cognitive control required by the underlying tasks. Within-domain IIV tapping cognitive control functions more closely was increased in AD and MCI versus HCS, and appears to constitute a potential marker for the detection of prodromal AD at the MCI stage. Across-domain IIV tapping less cognitive control functions was increased in AD versus MCI and HCS, and may detect incipient dementia and separate AD from the MCI stage.

The establishment of cognitive markers that accurately predict the diagnosis of AD and its preclinical manifestation MCI, supports the effort of early detection. Mean performance in tests of verbal episodic memory (Derby et al., 2013) and executive function (Schroeter et al., 2012) in particular are known markers for predicting AD. The reliable detection of early cognitive impairment based on mean cognitive performance in clinical routine, however, poses a challenge. Most importantly, cognitive changes in subjects with high educational background may be present prior to a clinical diagnosis but may be very subtle, and therefore may be undetected. Cognitive measures that discriminate between MCI due to AD and HCS based on abilities relevant to everyday life (i.e. Bird et al., 2010) might further support the reliable early detection, but such tests have not been under ample investigation. Across- and within-domain IIV was found to be independent from the mean cognitive performance, and might therefore represent a more sensitive early marker of cognitive impairment than mean cognitive performance.

Although it represents an easy to use measure in clinical routine (Holtzer et al., 2008) only a few studies have investigated IIV across accuracy scores from tests representing different cognitive domains in HCS and AD (Brewster et al., 2012; Christensen et al., 1999; Lindenberger & Baltes, 1997; MacDonald et al., 2012) or in HCS, MCI and AD (Tractenberg & Pietrzak, 2011). Even though IIV has been related to impaired cognitive control functions (MacDonald et al., 2009), we are not aware of any study investigating IIV across accuracy scores from tests uniquely representing cognitive control in these groups. Latency-based IIV has been suggested to be a more sensitive measure than accuracy-based IIV (Hultsch et al., 2000), and the direct comparison of our results with work on latency-based IIV is challenging. However, different studies have demonstrated a relationship between these measures (Hilborn et al., 2009; Hultsch et al., 2002). Accordingly, increased latency- and accuracy-based IIV have been linked to older age (Hilborn et al., 2009; Hultsch et al., 2002; Lövden et al., 2007; West et al., 2002), cognitive decline (Kliegel & Sliwinski, 2004; Lövden et al., 2007), and to predict probable AD (Brewster et al., 2012) and incident dementia (Holtzer et al., 2008). IIV has therefore widely been accepted as a stable trait (MacDonald, Nyberg, & Backman, 2006) - possibly reflecting central nervous system integrity (MacDonald et al., 2009). More precisely, evidence for a strong association between IIV and frontal gray and white matter integrity (Lövdén et al., 2013; Stuss, Murphy, Binns, & Alexander, 2003), and evidence of changed gray and white matter integrity in MCI and AD (Jackson et al., 2012; Radanovic et al., 2013;

Yang et al., 2012) support the idea of frontal system disruptions underlying increased IIV in dementia (Jackson et al., 2012).

It is beyond the aim of our study to draw direct inferences about the origins of IIV. However, consistent with our hypothesis and the literature (MacDonald et al., 2012; Tractenberg & Pietrzak, 2011), we found increased across-domain IIV in AD versus HCS and in AD versus MCI. Therefore, across-domain IIV was similar in MCI and HCS. Even though others have examined latency-based IIV within but not accuracy-based IIV across non-cognitive control tasks (Tales et al., 2012), they have also reported similar IIV in these groups. Moreover, MCI subjects who later converted to dementia were found to have higher IIV than non-converters. The absence of a group difference between MCI and HCS in our study may therefore be related to a low proportion of future converters in our MCI group. Additionally, and since higher IIV has been found in tasks requiring cognitive control (MacDonald et al., 2009), the requirement of cognitive control processes in the tasks underlying across-domain IIV might have been too limited to differentiate between these groups. Consistent with this assumption, and consistent with the literature on latency-based within-domain IIV (Duchek et al., 2009) we found within-domain IIV, and hence IIV across tasks placing more demands on cognitive control processes, being increased in MCI versus HCS. Considering impaired cognitive control functions in MCI and AD (Schroeter et al., 2012), one might have expected increased within-domain IIV in AD versus MCI. Against our expectations it was similar in both groups. Since the use of a high number of trials has previously been proposed to reliably detect IIV (Schmiedek, Lövdén, & Lindenberger, 2009), it might be less pronounced when computed across three accuracy scores only, even when computed across cognitively demanding tasks as in our study.

The similar difference scores in all groups offer additional support for increasing accuracy-based IIV across groups in general. Though not significantly different from the difference scores in HCS and AD, it was very small in MCI (M=0.005), reflecting the increase in within-domain IIV/stability in across-domain IIV between HCS and MCI. Due to the dependence of IIV on cognitive control tasks, higher within- than across-domain IIV may be expected. However, the higher across-domain IIV might be caused by the early deterioration of episodic memory (Albert et al., 2011) and short-term memory capacity (Schmitt et al., 2009) compared to other cognitive domains in the disease process. Consequently, and although mean performance was considered in the relevant analyses, the use of a verbal learning task and a task assessing short-term memory capacity might have triggered higher across-domain IIV.

Additionally, we found increased within-domain IIV in HCS ε4 carriers versus non-carriers, whereas there was no ε4-related change in IIV in the other groups. Our result is consistent with findings from Duchek et al. (2009) who have reported increased latency-based IIV in a cognitive control task, but similar IIV in tasks without cognitive control components in HCS ε4 carrier vs. non-carrier. Since the frontal lobe constitutes a brain region that manifests ε4-effects even early in the disease (Filbey et al., 2010), and is thought to be at the basis of IIV (MacDonald et al., 2009), the present findings offer further support for a relationship between within-domain IIV and APOE status. It may, however, well be that ε4-related change in IIV appears in HCS but may not be evident by the MCI and AD stage.

The major limitation of our study is related to the selection of the tasks. The limited number of available neuropsychological tests did not allow applying factor analyses. Hence, the tasks and their domain-relatedness were identified following the literature. Based on the high engagement of cognitive control processes, we identified executive function tasks to calculate within-domain IIV. However, cognitive control processes affect a wide range of cognitive functions. This is why we aimed to identify tasks placing low demands on cognitive control for across-domain IIV, and tasks placing high demands on cognitive control for within-domain IIV. This approach, however, revealed potential confounding factors which make it difficult to clearly determine whether our results can be attributed to the fact that IIV was calculated across versus within-domain, or to the fact that the underlying tasks elicited low versus high cognitive control. However, a higher number as well as a wider range of neuropsychological tests would be required to clearly differentiate between these aspects. Hence, only cautious conclusions can be drawn based on our results. Both aspects might be considered relevant with regard to across-domain IIV. More precisely, similar across-domain IIV between HCS and MCI is most likely based on equally reduced cognitive abilities across domains in MCI (see Table 1). Although cognitive control processes are expected to be impaired in prodromal AD, the low level of cognitive control processes elicited by these tasks may have been responsible for the uniformity of the decrease. The impairment of cognitive control processes, however, may have been sufficient to produce variation across tasks in AD (e.g. unequally decreased test performances in AD vs. MCI, see Table 1). In contrast, the aspect of high versus low cognitive control might be considered relevant with regard to within-domain IIV. Increased within-domain IIV in MCI is most likely based on unequally decreased performances in within-domain IIV tasks (see Table 1). If it was the across versus within-domain aspect that was critical, equally decreased performances could have been expected. Impaired cognitive control processes producing inconsistencies across performances in cognitive control sensitive tasks, and hence, producing higher within-domain IIV in MCI seem more plausible. The further reduction of cognitive control abilities in AD might lead to two different scenarios: a) further increased within-domain IIV due to inconsistent test performances or b) reduced within-domain IIV based on floor effects. Since tasks with potential floor effects were excluded, the latter does rather not apply. Although within-domain IIV did not differ significantly between MCI and AD, IIV was higher in AD (Figure 1), indicating further increasing IIV. The lack of a significant difference might indeed have been caused by the low sample size, and by the very subtle characteristic of within-domain IIV in general. The finding of higher across- than within-domain IIV across the groups in turn is most likely related to inconsistent performances across tests representing different cognitive domains. In summary, and although the present results must be interpreted with caution, our results indicate that the aspect of across versus within domain might be most relevant for the general characteristic of the IIV scores (higher across- than within-domain IIV). In contrast, the aspect of high versus low cognitive control might be at the basis of within-domain IIV group differences.

The minor limitations of our study are attributed to the cross-sectional design. Our results, therefore, do not permit to claim causality regarding the relationship between AD pathology and IIV. More precisely, it has been argued that cross-sectional data do not permit to clearly distinguish variability caused by aging or neurodegeneration from stable individual characteristics (Lindenberger & Potter, 1998). This risk was addressed by treating age and within- and across-domain IIM as covariates in all analyses. Furthermore,

most test performances underlying IIV were also used for diagnostic purpose, thus posing the risk of circularity. However, we assume the risk to be minimal, since the outcome of interest in the present study was the ISD calculated across tasks. In addition to that, neuropsychological tasks that had not been used for IIV calculation, wide-ranging medical information, and clinical evaluation also contributed to the diagnosis. Another limitation is related to the multidimensional nature of the neuropsychological tasks. Although the tasks which were used to calculate within-domain IIV place high demands on cognitive control processes, they do not exclusively assess this particular cognitive function. Processing speed (Greenaway, Smith, Tangalos, Geda, & Ivnik, 2009), inhibition (Troyer et al., 2006) and visuo-construction (Lezak et al., 2004) represent further cognitive abilities that are crucial for successfully performing the Letter Fluency task, the Stroop Test and the Five-Point Test, respectively. They might, therefore, represent potential confounders in the present study. Since the tasks which were used to calculate across-domain IIV, however, place fewer demands on cognitive control processes than the task which were used to calculate within-domain IIV, we assume this risk to be reduced.

Despite these limitations, and although comparison with other studies may be limited due to methodological differences among studies (e.g. IIV definition and measures, diagnostic criteria), the present study offers further support for increased IIV in MCI and AD in general, and for increased accuracy-based IIV in particular. From a clinical point of view, accuracy-based IIV may be more useful than latency-based IIV measures in everyday clinical routine. First, tasks assessing cognitive control functions and non-cognitive control functions are usually included in standard clinical neuropsychological test batteries, and therefore allow IIV calculations without applying additional tests. Second, assessing accuracy-based IIV avoids the necessity to add multiple trials or blocks of the same task to the standard test battery, and therefore reduces the burden for the patients in dementia diagnostics. The present study, therefore, underscores the importance of considering the value of IIV in the early detection of prodromal AD and demonstrates the usability of accuracy-based IIV measures in AD diagnosis. Both across- and within-domain IIV may represent potential cognitive markers for the early detection of prodromal AD. However, further examination by using a higher number of more complex tests in a longitudinal design is needed to provide more specific information about the predictive value of these IIV scores.

5.2 Study 2: Intraindividual variability and gray matter volumes in future Alzheimer's disease patients

Intraindividual variability across cognitive tasks is not increased and not related to gray matter volumes in Alzheimer's disease patients at predementia stage

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5.2.1 Abstract

Potential treatments for Alzheimer's disease (AD) may be most effective in prodromal stages, referred to as mild cognitive impairment (MCI). However, there is heterogeneity among MCI, with only some patients progressing to AD. Thus, the establishment of biomarkers that identify future converter to AD is crucial. Previous results from our group have indicated that cognitive intraindividual variability (IIV) across accuracy scores from cognitive control tasks (within-domain IIV) might represent an early marker for AD. Furthermore, although IIV across reaction time tasks has been associated with prefrontal and parietal gray matter volumes, neuronal correlates of IIV across accuracy score, and hence, of within-domain IIV are unknown. With the present study, we aimed to further investigate the potential value of within-domain IIV acting as early marker for AD, and to examine its relationship with gray matter volumes. For this purpose, we examined the correlation between within-domain IIV and volumes of IIV-relevant brain regions such as dorsolateral- and ventrolateral prefrontal (dlPFC, vlPFC) as well as posterior parietal cortices (PPC) in patients with stable MCI (MCI-S, n=18), future converter at baseline (MCI-CB, n=10) and healthy control subjects (HCS), and the ability of within-domain IIV to predict diagnostic group membership. However, within-domain IIV was similar in MCI-S and HCS, and more importantly in MCI-CB and HCS, preventing us from performing logistic regression analyses. Furthermore, we did not observe significant relationships between within-domain IIV and gray matter volumes in either of the groups. Our results, therefore, not only contradict the assumption of prefrontal and parietal gray matter volumes being related to within-domain IIV in MCI but limit the potential of within-domain IIV as early marker for AD. However, the low characterization of within-domain IIV in rather small samples may have essentially influenced the present results. We propose further studies with larger cohorts to further examine within-domain IIV as a predictor for AD, and studies including AD patients to examine the relationship between within-domain IIV and gray matter volumes.

5.2.2 Introduction

Evidence for treatment methods being most efficacious in preclinical or early disease stages (Golde et al., 2011; Sperling, Jack, et al., 2011) has increased the importance of reliable methods for the early detection of Alzheimer's disease (AD) and its preclinical manifestations, referred to as mild cognitive impairment (MCI). Although MCI subjects of the amnestic subtype (aMCI) are more likely to progress to AD than subjects of the non-amnestic subtype (Roberts et al., 2014), there is heterogeneity even among aMCI. Some patients develop different forms of dementia than AD, whereas others remain stable for a long time, and still others may even reveal normal cognitive abilities again (Roberts et al., 2014). The establishment of markers that accurately identify future converter to AD is therefore crucial.

Cognitive intraindividual variability (IIV) has evidenced representing a potential marker of early cognitive impairment (MacDonald et al., 2009), with IIV across multiple trials of a reaction time (RT) task or across different RT tasks (latency-based IIV) predicting mild cognitive impairment (Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010; Cherbuin, Sachdev, & Anstey, 2010), and being increased in MCI (Christensen et al., 2005; Dixon et al., 2007; Duchek et al., 2009; McLaughlin et al., 2010; Strauss et al., 2007) and AD (Hultsch et al., 2000; Jackson et al., 2012; Rochat et al., 2013). However, integrating repetitive RT tasks into already existing comprehensive test batteries may increase the testing-associated burden on patients. Although IIV across accuracy scores of different cognitive tasks (accuracy-based IIV) may provide an uncomplicated alternative, it has not been investigated extensively. Nonetheless, the use of accuracy-based IIV across tests representing different cognitive domains (across-domain IIV) has been promising for predicting global (Kliegel & Sliwinski, 2004) and functional decline (Morgan et al., 2012), incident dementia (Holtzer et al., 2008) and probable AD (Vaughan et al., 2013). Likewise, it was found to be increased in MCI and AD (Kälin et al., 2014; MacDonald et al., 2012; Tractenberg & Pietrzak, 2011). IIV has been proposed to index cognitive control processes (MacDonald et al., 2009). Results from our previous study investigating accuracy-based IIV across tests placing high demands on cognitive control processes (within-domain IIV) have supported the idea of a breakdown of cognitive control functions leading to increased within-domain IIV in MCI and AD when compared with healthy control subjects (HCS) (Kälin et al., 2014). Thus, increased within-domain IIV may represent an early marker for AD. With the present study, we aimed to further verify the potential value of within-domain IIV as early marker for AD, and to obtain further information about neuronal correlates of within-domain IIV.

Despite the growing number of IIV studies, little is known about its structural brain correlates. Cognitive control processes, and hence IIV are thought to be supported by the frontal cortex (MacDonald et al., 2009) in general, and by dorsolateral and ventrolateral prefrontal cortices (dlPFC; vlPFC) in particular (Casey, Nigg, & Durston, 2007; Levy & Wagner, 2011; Liston et al., 2006; Miller & Cohen, 2001; Weissman et al., 2006). Other regions outside of the frontal lobe that have been associated with cognitive control processes include parietal cortex regions (Wilk et al., 2012). Correspondingly, in agreement with

studies associating white matter integrity with reaction time performance (Bender & Raz, 2012; Madden et al., 2004), different studies have evidenced an association between latency-based IIV and white matter alterations in temporal (Ullen, Forsman, Blom, Karabanov, & Madison, 2008), parietal (Bellgrove, Hester, & Garavan, 2004; Jackson et al., 2012; MacDonald, Nyberg, Sandblom, Fischer, & Bäckman, 2008; Ullen et al., 2008; Wilk et al., 2012) and frontal regions in general (Bunce et al., 2007; Lövdén et al., 2013), and prefrontal cortex (Ullen et al., 2008), dlPFC and vlPFC (Jackson et al., 2012) in older age in particular. Although findings of higher latency-based IIV in subjects with frontal lobe dementia (Murtha, Cismaru, Waechter, & Chertkow, 2002) and in subjects with dlPFC lesions (Stuss et al., 2003) have indicated a link between gray matter alterations and increased latency-based IIV as well, different studies have failed to observe such a relationship (Lövdén et al., 2013; Moy et al., 2011; Ullen et al., 2008; Walhovd & Fjell, 2007). Less is known about structural correlates of accuracy-based IIV. Only Lövdén et al. (2013) have examined the relationship between accuracy-based IIV and white as well as gray matter volumes in cognitively normal subjects. The authors have reported a relationship between dlPFC gray matter volume and IIV, but not between frontal white matter and IIV, therefore providing support for a potential relationship between accuracy-based IIV and gray matter volumes in IIV-relevant regions.

Given the increasing support for higher IIV in MCI (e.g. McLaughlin et al., 2010) and AD (e.g. Kälin et al., 2014), it is surprising that only a few studies have investigated structural correlates of IIV in AD. So far, relationships have only been reported between latency-based IIV and white matter volumes in dlPFC, vlPFC, superior frontal gyrus and corpus callosum in MCI and mild AD (Anstey et al., 2007; Jackson et al., 2012). However, and to our knowledge, there has been no study investigating the relationship between accuracy-based IIV and gray matter alterations in MCI. Cortical brain atrophy due to early involvement of neurofibrillary tangle formation followed by neuronal loss has repeatedly been related to increasing cognitive impairment in MCI and AD (e.g. Carter et al., 2014). Apart from memory impairment (Bollo-Gasol, Pinol-Ripoll, Cejudo-Bolivar, Llorente-Vizcaino, & Peraita-Adrados, 2014), executive dysfunction in general (e.g. da Costa Armentano et al., 2013), and reduced cognitive control processes (Rapp & Reischies, 2005; Schroeter et al., 2012) in particular represent early clinical signs of the disease. A relationship between prefrontal cortex volumes and within-domain IIV is therefore highly likely.

Accordingly, we aimed to investigate the relationship between within-domain IIV and regional gray matter volumes. We correlated within-domain IIV and volumes of IIV-relevant brain regions in aMCI who remained cognitively stable (MCI-S), aMCI with future worsening of cognitive functions and conversion to AD (MCI-CB) and HCS to gain more information about neuronal correlates of within-domain IIV in AD pathology. We furthermore aimed to obtain more information about within-domain IIV acting as potential early marker for AD. To this end, we explored the contribution of within-domain IIV to predict membership to diagnostic groups. We hypothesized a negative relationship between within-domain IIV and gray matter volumes of IIV-relevant brain regions in MCI-CB but not MCI-S, and within-domain IIV contributing to the prediction of MCI-CB but not MCI-S membership.

5.2.3 Methods

Participants

We selected participants from pre-existing longitudinal cohorts at the Memory Clinic of the Division of Psychiatry Research and Psychogeriatric Medicine, University of Zurich. MCI was diagnosed according to Winblad et al. (2004) after a comprehensive clinical and neuropsychological work-up. Conversion to dementia was diagnosed when subjects met National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984) criteria for probable AD. All diagnoses were made by a multidisciplinary team under the supervision of an experienced psychiatrist.

For the present study, inclusion criteria for MCI subjects were: diagnosis of aMCI and availability of magnetic resonance imaging (MRI) as well as cognitive data at baseline. Exclusion criteria were: MR exclusion criteria, left-handedness, evidence for the use of psychoactive medication, abuse of alcohol and drugs, other past or present psychiatric or neurological diseases or significant other systemic diseases, or MRI findings of infarction or other focal lesions, multiple lacunes or lacunes in critical memory structures. A total of 46 baselines from subjects with aMCI were considered for the present study. From this sample, 8 subjects were excluded from the analyses due to left-handedness (n=5), structural abnormalities in the brain (n=1), and T1 parameters that were inconsistent with the MRI study protocol (n=2). Due to a change in test batteries, 10 MCI subjects were missing a cognitive test score relevant for computing IIV, and were excluded from the analyses. The remaining population at baseline was then stratified into two subgroups according to longitudinal clinical information; subjects who remained cognitively stable during an approximately 2-year follow-up (MCI-S, n=18), and subjects with future worsening of cognitive impairment and conversion to probable AD within the 2-year follow-up (MCI-CB, n=10). Inclusion criteria for HCS were: stable cognitive health ascertained by clinical work up and neuropsychological testing during a roughly 2-year follow-up, age between 59 and 87. Exclusion criteria were: MRI exclusion criteria, left-handedness, evidence for abuse of alcohol and drugs, psychiatric or neurological diseases or significant other system diseases. HCS were identified for group wise age and gender matching with MCI-S and MCI-CB, respectively. The neuropsychological test battery consisted of multiple tests covering the following cognitive domains: episodic memory, executive function, attention/psychomotor speed, language and visual-constructive abilities. Impairment was defined if at least one score per domain was 1.5 standard deviations (SD) below group means provided by test-specific normative data.

Accordingly, a total of 18 MCI-S and 10 MCI-CB, as well as age and gender matched HCS were considered for the current analysis. The final demographic details are presented in Table 3. This study was approved by the cantonal ethics committee of canton Zurich, Switzerland, in accordance with the Helsinki Declaration. All participants provided written informed consent prior to study inclusion.

Computation of intraindividual variability

For calculating within-domain IIV, we used accuracy scores from three tests, each representing executive functions and eliciting recruitment of cognitive control processes. The rationale behind the selection of the tasks has been described in detail elsewhere (Kälin et al., 2014). Briefly, we identified tasks with less than 1% missing values, and with no ceiling or floor effects to prevent suppressing variation at the extreme ends of the distribution. Therefore, we used accuracy scores from the Letter Fluency test (letter S), Trial 3 from the Stroop Test (Troyer et al., 2006) and the Five-Point Test (Regard et al., 1982).

The simplest method to compute IIV is to calculate the intraindividual standard deviation (ISD) (Nesselroade & Salthouse, 2004) across each individual's accuracy scores. Before computing ISD, one missing Stroop Test score in HCS and one missing Letter Fluency test score in MCI were imputed with the expected-maximization algorithm in SPSS. Then, the accuracy scores were *z*-transformed based on the mean and standard deviation of the pooled sample (MCI-S, MCI-CB, and HCS). The *z*-scores from the Stroop Test were multiplied by -1 to adjust for scaling difference. We then computed ISD across each individual's *z*-transformed accuracy scores on Letter Fluency, Stroop Test, and Five-Point Test representing within-domain IIV. To address the association between ISD and mean performance (Allaire & Marsiske, 2005), we used the intraindividual mean (IIM) across *z*-transformed accuracy scores from tests underlying within-domain IIV (within-domain IIM) as covariate in all relevant analyses.

Magnetic resonance image acquisition and processing

All subjects were scanned on the same 1.5 Tesla Phillips Achieva scanner using an 8-element head coil. Whole-brain high-resolution three-dimensional (3D) T1-weighted structural data was obtained by using the following scanning parameters: 166 slices, repetition time: 6.9 milliseconds, echo time: 3.2 milliseconds, flip angle: 8°, field of view: 240 x 240 x 166 millimeters (anterior-posterior, foot-head, right-left), slice thickness: 1 millimeter, total scan time: 15 min.

All volume measures were estimated by using the fully automated CIVET pipeline (version 1.1.10; Montreal Neurological Institute McGill University, Montreal, Quebec, Canada) (Ad-Dab'bagh et al., 2006). Briefly, magnetic resonance images of each subject were first linearly registered to the standard stereotaxic ICBM152 template (Collins, Neelin, Peters, & Evans, 1994; Mazziotta et al., 2001). Images were corrected for intensity nonuniformity resulting from inhomogeneity in the magnetic field (Sled, Zijdenbos, & Evans, 1998). Skulls were stripped from the brain tissue (Smith, 2002), and segmentation into white matter, grey matter, and cerebrospinal fluid (CSF) was achieved using the Intensity-Normalized Stereotaxic Environment for Classification of Tissues (INSECT) algorithm (Tohka, Zijdenbos, & Evans, 2004; Zijdenbos, Forghani, & Evans, 1998). Regional gray matter volume measures along the cortical surface were then estimated using the intersection of the gray matter classification provided by CIVET and the LONI Probabilistic Brain Atlas (LPBA40) (Shattuck et al., 2008) in MNI space. These delineations were then transformed back into native space by using an inverse linear transformation (ANIMAL) (Collins, Holmes, Peters, & Evans, 1995) resulting in volumes of 40 cortical regions per hemisphere. Furthermore, total incranial volume (eTIV) was estimated following a previously validated procedure (Buckner et al., 2004).

Volumes of interest in both hemispheres were achieved by combining regional volumes obtained from the CIVET pipeline. Dorsolateral prefrontal cortex volumes were acquired by combining volumes of the middle and superior frontal gyrus. These regions largely cover Brodmann Areas (BA) 8, BA9 and BA46, areas that have previously been used for dlPFC definition (Burgmans et al., 2009; Clerx et al., 2013; Echavarri et al., 2011; Tisserand et al., 2002). Ventrolateral prefrontal cortex volumes were obtained using inferior frontal gyrus volumes approximately covering BA44, BA45 and BA47 (Badre & Wagner, 2007; Levy & Wagner, 2011). Posterior parietal cortex volumes included volumes of supramarginal and angular gyrus as well as precuneus, covering BA7, BA39 and BA40 (Francois-Brosseau et al., 2009; Vingerhoets, 2014). Since previous studies have reported no relationship between accuracy- and latency-based IIV and gray or white matter volumes in occipital regions (Bunce et al., 2007; Lövdén et al., 2013), the occipital lobe was selected as control region. Its volume was acquired by summarizing superior, middle and inferior occipital gyrus, cuneus and lingual gyrus volumes (Shattuck et al., 2008).

Statistical analyses

Group comparisons (MCI-S versus HCS; MCI-CB versus HCS) of normally distributed demographic data and cognitive raw scores were applied using analysis of variance (ANOVA). Mann-Whitney U tests were performed to compare variables without a normal distribution. Pearson's chi-square test was used for categorical variables. The relationship between raw gray matter volumes and within-domain IIV was explored by performing Pearson's correlation across diagnoses within each group (Group 1: MCI-S and HCS; Group 2: MCI-CB and HCS), and by controlling for influences of age, gender, and within-domain IIM. Subsequent group comparisons (MCI-S versus HCS; MCI-CB versus HCS) of raw volumes were investigated by applying ANOVA, whereas differences in within-domain IIV were performed using univariate analyses of covariance (ANCOVA) with diagnostic group treated as the main effect and within-domain IIM as a covariate. The planned logistic regression analysis to test the ability of within-domain IIV to predict diagnostic group membership was not performed due to the lack of significant group difference. All volume analyses were repeated by using volumes relative to eTIV (volume / eTIV * 100) in order to adjust volumes for individual differences in head size. Tests were performed with a significance level of $p < 0.05$. Statistical analyses were performed by using the statistical analysis software package IBM SPSS statistics 21 for windows.

5.2.4 Results

A segmentation map of the summarized regions of interest for volumetric analyses is shown in Figure 2. Descriptive statistics for demographic information, cognitive raw scores as well as raw volumes and volumes relative to eTIV is listed in Table 3. Compared to HCS, neither of the patient groups differed on mean age, years of education or gender. Both patient groups demonstrated significantly lower MMSE scores than their HCS matches (Group 1 U=69.00, p=.001; Group 2 U=21.00, p=.025).

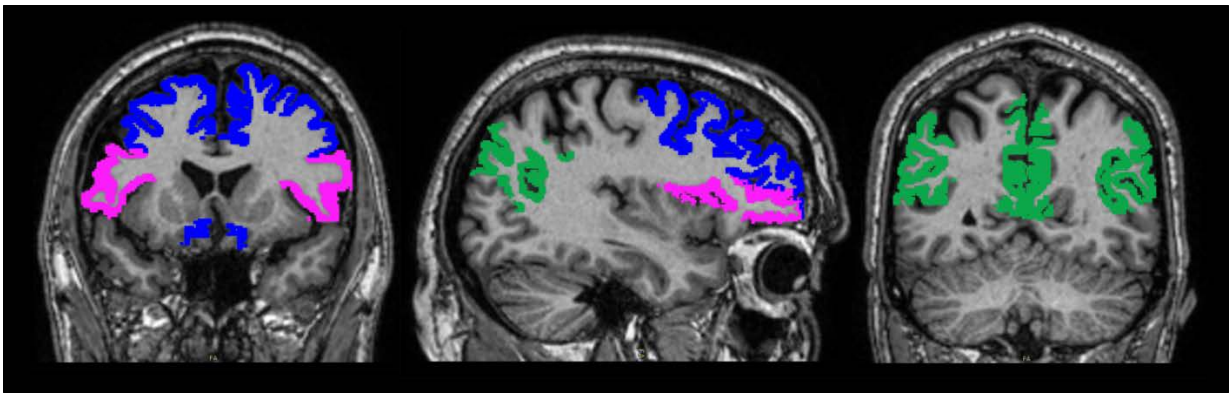

Figure 2 Regions of interest that were automatically segmented, namely: ventral lateral prefrontal cortex (pink), dorsolateral prefrontal cortex (blue); posterior parietal cortex (green) in a healthy control subject (male, 69 years of age).

Primary analyses

The correlation coefficients representing the association between gray matter volumes relative to eTIV and within-domain IIV across diagnosis within each group are presented in Table 4. Confirming our assumption, within-domain IIV was not significantly correlated with any of the volumes of IIV-relevant regions in Group 1. Contrary to our expectation, the same was true for Group 2, where none of the correlations were significant as well. Correlation analyses were repeated across all groups (MCI-S, MCI-CB, and HCS). Again, analyses revealed no significant correlations (data now shown). Correlation coefficients were similar when statistical analyses were performed by using raw volumes instead of volumes relative to eTIV (Table 4).

Before logistic regression analysis was performed to investigate the ability of within-domain IIV predicting diagnostic group membership, we performed group-wise comparisons. These results together with raw scores of cognitive tests are presented in Table 3. Confirming our assumption, within-domain

IIV was similar in MCI-S compared to HCS. Against our expectation, however, the same was true for the comparison of within-domain IIV between MCI-CB and HCS. The analyses were repeated by pooling MCI subjects (MCI-S and MCI-CB versus HCS). However, within-domain IIV was still similar in pooled MCI and HCS (data not shown). Based on these result, we refrained from performing the planned logistic regression analysis.

However, and compared to HCS, MCI-S performed significantly worse in the Letter Fluency test ($F(1,34)=4.85$, $p=.035$) and Stroop Trial 3 ($F(1,27=6.54$, $p=.016$) but equal in the Five-Point test. Accordingly, within-domain IIM was significantly lower in MCI-S compared to HCS ($F(1,27=10.72$, $p=.003$). Similarly, MCI-CB performed significantly worse in Stroop Trial 3 compared to HCS ($F(1,27=6.54$, $p=.037$). Additionally, they performed significantly lower in the Five-Point test ($U=19.5$, $p=.019$) but equally in the Letter Fluency test when compared with HCS. There was only a tendency towards reduced within-domain IIM in MCI-CB ($F(1,12)=4.63$, $p=.05$).

Secondary analyses

Based on absent significant relationships between within-domain IIV and gray matter volumes, we performed group wise comparisons of dlPFC, vlPFC and PPC volumes. Results of the comparison of volumes relative to eTIV between groups (MCI-S versus HCS; MCI-CB versus HCS) together with raw volumes of bilateral structures are shown in Table 3. There were no volumetric differences in any of the examined IIV-relevant regions or in eTIV in MCI-S when compared with HCS. Against our expectation, though, volume sizes of IIV-relevant regions and eTIV did not differ between MCI-CB and HCS as well. Again, analyses were repeated by comparing volumes between pooled MCI groups and HCS. All volumes, however, were similar in MCI and HCS (data not shown). Significance and *p*-values were similar when statistical analyses were performed by using raw volumes instead of volumes relative to eTIV (Table 3).

Table 3 Demographic data, cognitive variables and gray matter volumes for patient and control groups

	Group 1				Group 2			
	HCS		MCI-S	*p*	HCS		MCI-CB	*p*
N	18		18		10		10	
Age, years	70.22	5.97	69.83	6.31	.850	75.10	5.61	75.10	5.81	.399
Education, years	16.67	2.42	14.33	3.10	.722	14.50	3.63	13.20	3.08	1.000
Gender, M/F	9/9		8/10		1.000	3/7		2/8		1.000
MMSE, /30	29.83	0.83	28.56	1.34	.001*	29.10	0.99	27.20	0.21	.025*
Follow-up time, months[a]	33.56	29.70	23.61	7.92	N/A	28.60	22.09	18.00	8.99	N/A
Cognitive variables, raw scores										
Letter Fluency	33.67	11.76	25.33	10.94	.035*	23.80	5.55	21.80	11.42	.627
Stroop Trial 3	25.39	6.68	33.44	11.57	.016*	27.50	3.75	34.80	9.53	.037*
Five-Point Test	27.83	6.99	23.11	7.82	.065	24.20	4.44	17.50	6.50	.019*
Within-domain IIM[b]	.54	0.47	-.21	0.83	.003*	.01	0.36	-.60	0.83	.052
Within-domain IIV[c]	.89	0.24	.84	0.24	.553	.45	0.30	.51	0.30	.653
Gray matter volumes mm^3										
dlPFC, right	52097.51	5554.77	50798.15	6109.52	.509	50752.01	4276.84	49364.09	4734.51	.500
dlPFC, left	53673.68	5903.61	52155.13	7673.62	.510	50989.75	3732.99	49732.05	6601.17	.608
vlPFC, right	12069.73	1588.35	11894.94	1492.27	.377	11947.23	1546.41	11634.35	1682.34	.971
vlPFC, left	12344.50	1611.27	12096.84	1892.16	.501	11695.27	1015.71	11368.07	1744.71	.615
PPC, right	24769.46	2799.54	24144.33	3218.36	.584	24571.89	2725.29	23201.51	2582.23	.263
PPC, left	27068.52	3578.09	25010.16	3108.07	.236	24911.79	2582.56	24848.20	3558.62	.964
Occipital lobe, right	36904.65	4164.51	37230.61	5695.95	.060	35860.06	4152.95	34910.53	3364.38	.796
Occipital lobe, left	38169.52	4698.55	35612.29	5084.22	.363	34557.54	4333.59	34586.04	4080.23	.988

*Gray matter volumes (volume/eTIV * 100)*								
eTIV, cm^3	1602.97	157.94	1539.31	169.61	.252	1503.95	155.73	1481.33	145.67	.741
dlPFC, right	3.25812	.26405	3.30174	.21124	.588	3.38728	.24336	3.35155	.37380	.803
dlPFC, left	3.35728	.29285	3.38312	.29080	.792	3.40575	.24641	3.37257	.46176	.843
vlPFC, right	.75415	.07304	.77292	.05089	.377	.79537	.07343	.78557	.08363	.784
vlPFC, left	.76987	.05715	.78420	.06876	.501	.78211	.07780	.76735	.08598	.692
PPC, right	1.54709	.10966	1.56936	.13136	.584	1.63894	.14880	1.57262	.17251	.369
PPC, left	1.68992	.15715	1.62876	.14696	.236	1.66224	.15360	1.68428	.23238	.805
Occipital lobe, right	2.30491	.14996	2.41317	.18206	.060	2.38577	.13007	2.36839	.24287	.844
Occipital lobe, left	2.37965	.14123	2.31786	.24668	.363	2.29971	.19781	2.34336	.26075	.678

Note. HCS = healthy control subjects; MCI-S = stable mild cognitive impairment at baseline; MCI-CB = mild cognitive impairment converter at baseline; IIM = intraindividual mean; IIV = intraindividual variability; eTIV = estimated total intracranial volume; dlPFC = dorsolateral prefrontal cortex; vlPFC = ventral lateral prefrontal cortex; PPC = posterior parietal cortex; MMSE = Mini Mental State Examination; N/A = not applicable. Values are means and standard deviations unless specified otherwise. * Significant *p* value test by analysis of variance (normally distributed data), Mann U Whitney (not normally distributed data), and Pearson's X^2 test (categorical variables) unless specified otherwise. [a] Follow-up times were calculated as follows: the time from baseline MRI to the time of Alzheimer's disease diagnosis for MCI-CB, the time from baseline MRI to the last available visit for MCI-S, and the time from the first HCS diagnosis to the last available visit for HCS. [b] Mean across *z*-transformed cognitive scores from tests underlying within-domain IIV. [c] Intraindividual standard deviation across *z*-transformed cognitive scores, *p* value test by analyses of covariance, means adjusted for within-domain intraindividual mean.

Table 4 No correlation between gray matter volumes and within-domain IIV

	Group 1 (HCS=18; MCI-S=18)	Group 2 (HCS=10; MCI-CB=10)
	Within-domain IIV	*Within-domain IIV*
Gray matter volumes mm^3		
dlPFC, right	.155	.135
dlPFC, left	.090	.177
vlPFC, right	.290	.120
vlPFC, left	.216	- .022
PPC, right	.164	- .122
PPC, left	.171	.042
Occipital lobe, right	- .082	.385
Occipital lobe, left	- .013	.163
*Gray matter volumes (volume/eTIV*100)*		
dlPFC, right	.151	- .028
dlPFC, left	.090	.047
vlPFC, right	.308	- .035
vlPFC, left	.258	- .239
PPC, right	.091	- .378
PPC, left	.060	- .076
Occipital lobe, right	- .018	.371
Occipital lobe, left	- .165	.067

Note. HCS = healthy control subjects; MCI-S = stable mild cognitive impairment at baseline; MCI-CB = mild cognitive impairment converter at baseline; IIV = intraindividual variability; dlPFC = dorsolateral prefrontal cortex; vlPFC = ventral lateral prefrontal cortex; PPC = posterior parietal cortex. Values represent correlation coefficients. Volumes were correlated with within-domain IIV by applying Pearson's correlation in pooled groups by controlling for age, gender, and within-domain intraindividual mean.

5.2.5 Discussion

With the present study, we aimed to obtain more information about neural correlates of within-domain IIV and of its potential as early marker for AD. However, we found no significant relationship between within-domain IIV and gray matter volumes in any of the brain regions relevant for IIV (dlPFC, vlPFC, PPC) in MCI-S and HCS, or in MCI-CB and HCS. Additionally, within-domain IIV was found to be similar not only in MCI-S and HCS but also in MCI-CB and HCS.

The present result of similar within-domain IIV in MCI-CB and HCS are in contrast with results from our previous study where within-domain IIV was increased in MCI compared to HCS (Kälin et al., 2014). The lack of a significant difference between MCI-CB and HCS in the present study may, therefore, indicate that increased within-domain IIV is not a general characteristic of MCI due to AD but of cognitive impairment per se. The subsequently performed comparison of within-domain IIV between pooled MCI patients and HCS, however, again showed no significant difference. Another possible explanation for contradicting results may be the variation of the sample between the two studies. The previous study comprised MCI subjects of both, the aMCI and non-amnestic subtype (nMCI), whereas only aMCI subjects were included in the present study. It could be argued that the presumably lower range of cognitive impairments in current MCI groups has limited the range of IIV in the present study, particularly when considering the within-domain aspect of IIV. More precisely, and assuming impaired memory but unimpaired executive functions in aMCI, IIV across tasks representing executive functions may be lower in these subjects. This however renders unlikely considering the fact that 89% of aMCI in the present study showed impairments in multiple cognitive domains, and taking into account the rather low percentage of nMCI in our previous study (13%). We assume it more likely that the absent increase of within-domain IIV in MCI-CB is related to the small sample size on the one hand, and to the low characteristic utility of accuracy-based IIV on the other hand.

More precisely, although there has been no other study investigating accuracy-based IIV similar to our within-domain IIV, increased accuracy-based IIV has been observed in MCI compared to HCS in a study from Tractenberg and Pietrzak (2011). Others, however, have failed to observe increased accuracy-based IIV in MCI (Ramratan et al., 2012). Interestingly, and although accuracy-based IIV has failed to predict MCI by in a study from Vaughan et al. (2013), it has successfully predicted probable AD in the same study. These results fit into the row of other studies reporting increased accuracy-based IIV predicting incident dementia (Holtzer et al., 2008) and being higher in AD than in HCS (Kälin et al., 2014). At the same time, these results indicate that in MCI, accuracy-based IIV in general might be of low characteristic. Although a relationship between accuracy- and latency-based IIV has been reported (Hilborn et al., 2009; Hultsch et al., 2002), latency-based IIV has previously been reported a more sensitive measure than accuracy-based IIV (Hultsch et al., 2000). Supporting the higher sensitivity of latency-based IIV, Ramratan et al. (2012) have found higher latency- but not accuracy-based IIV in MCI. If the rather small difference of within-domain IIV between MCI (n=31) and HCS (n=149) (p=.05) in the previous study is additionally taken into consideration, it seems likely that the occurrence of a significant effect in those groups is highly dependent from the sample size. Hence, it seems as if much larger sample

sizes are required to observe a stable effect. In sum, it seems most likely that the lack of a difference of within-domain IIV between MCI-CB and HCS is related to the low characteristic utility of accuracy-based IIV in combination with rather low sample sizes.

The lack of a significant relationship between within-domain IIV and volumes of IIV-relevant regions such as the dlPFC, vlPFC and PPC in turn is most likely related to the low characteristic of both within-domain IIV and gray matter atrophy in these regions of interest. Neurofibrillary tangle formation in these regions occurs at rather late histopathological disease stages (Braak & Braak, 1990). Subjects at such early stages as MCI-CB may, therefore, still be free of pronounced frontal and parietal gray matter shrinking. Correspondingly, gray matter volumes of dlPFC, vlPFC and PPC were not only similar in MCI-S and HCS, but also in MCI-CB and HCS. Nevertheless, results from studies investigating gray matter atrophy in MCI have reported inconsistent results. Some studies have indeed observed reduced volumes of prefrontal (Han et al., 2012; Mosconi, Andrews, & Matthews, 2013; Zhao et al., 2014) and parietal cortex regions (Clerx et al., 2013; Zhao et al., 2014) in MCI, as well as reduced vlPFC (Bell-McGinty et al., 2005) and prefrontal cortex volumes (Burgmans et al., 2009) in MCI who later converted to dementia when compared to non-converter. Others, however, have failed to observe volume differences in parietal regions in MCI compared to HCS (Zhang et al., 2013), or in dlPFC when comparing future converter to non-converter (Burgmans et al., 2009). These inconsistencies are most likely related to sample variations, differences in the definition of the sample (MCI, converter and non-converter) and hence, in different disease stages of the included subjects.

Regardless of whether early atrophy in prefrontal or parietal cortex regions is existent or not, the present results do not support our assumption of within-domain IIV being related to the investigated gray matter volumes. To our knowledge, there has been no other study investigating this relationship in MCI or AD. By using different measurements of IIV, other studies have indeed observed a relationship between IIV and gray matter volumes of prefrontal cortex regions. Specifically, one study has reported a significant relationship between dlPFC gray matter volume and accuracy-based IIV in HCS (Lövdén et al., 2013), and two studies have reported higher latency-based IIV in patients with lesions in the dlPFC (Stuss et al., 2003) and patients with frontotemporal dementia (Murtha et al., 2002). However, other studies have failed to observe similar associations (Lövdén et al., 2013; Moy et al., 2011; Ullen et al., 2008; Walhovd & Fjell, 2007). At the time being, neither the literature nor the present results allow general conclusions about gray matter volumes representing structural brain correlates of accuracy-based IIV in general, and within-domain IIV in particular. Based on the present results, however, we can conclude that such a relationship does not exist in MCI-S or MCI-CB.

We have already discussed the limiting influences of early disease stages, relatively small subject numbers and the low characteristic utility of within-domain IIV on our analyses. The unknown number of HCS that will convert to MCI and of MCI-S that will convert to AD in the future represents another limiting factor of the present study. Despite the rather high mean follow-up times (see Table 3) in both groups, we cannot rule out the possibility of future conversions. Furthermore, the comparison of our results with the IIV literature is complicated by varying definition of accuracy-based IIV across studies. We calculated IIV across accuracy scores obtained from tasks eliciting cognitive control processes and

representing executive functions (within-domain IIV). Others have calculated IIV across accuracy scores from tasks representing different cognitive domains (across-domain IIV) (Holtzer et al., 2008; Kälin et al., 2014; MacDonald et al., 2012; Tractenberg & Pietrzak, 2011; Vaughan et al., 2013) or across accuracy scores from tasks representing the same domain, but not executive functions (Ramratan et al., 2012). Although there is yet no empirical basis for this assumption, within- and across-domain IIV may represent different measurements (for a discussion see Kälin et al., 2014), and the comparison of results across IIV studies poses a challenge.

We conclude that the potential value of within-domain IIV as early marker for AD is questionable. Studies consisting of much higher sample sizes compensating for the low characterization of within-domain IIV may provide further information. Within-domain IIV, however, does not seem to be associated with prefrontal and parietal gray matter cortex volumes in MCI-CB. Additional research including AD patients showing further progressed atrophy is required to investigate the relationship between within-domain IIV and AD related gray matter atrophy in IIV-relevant brain regions.

5.3 Study 3: Subcortical shape changes in future Alzheimer's disease patients

Subcortical shape changes, hippocampal atrophy and cortical thinning in future Alzheimer's disease patients

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5.3.1 Abstract

Treatment methods currently under investigation at onset of prodromal stages of Alzheimer's disease (AD) will require biomarkers that differentiate between patients with stable mild cognitive impairment and patients who will convert to AD in the future. Here, we applied recently developed analyses techniques to investigate differences in subcortical shape and volume alterations in patients with stable mild cognitive impairment (MCI-S, n=23, age range 59-82, 47.8% female), future converters at baseline (MCI-CB, n=10, age range 66-84, 90% female) and at time of conversion (MCI-CC, age range 68-87) compared to group-wise age and gender matched healthy control subjects (HCS, n=23, age range 61-81, 47.8% female; n=10, age range 66-82, 80% female; n=10, age range 68-82, 70% female). Additionally, sophisticated analyses techniques were used to further confirm cortical thinning and global and local measures of hippocampal atrophy as these are known key imaging markers for AD. Apart from bilateral striatal volume reductions, no morphometric alterations were found in MCI-S. In contrast, we identified shape alterations in striatal (caudate head, caudate body, ventral medial and ventral lateral putamen) and thalamic regions (anterior, posterior and medial dorsal thalamus) in MCI-CB and MCI-CC. The shape alterations were paralleled by AD-like patterns of left hemispheric morphometric changes (cortical thinning in medial temporal regions, hippocampal total and subfield atrophy) in MCI-CB with progression to similar right hemispheric alterations in MCI-CC. The present results further confirm the key role of early cortical thinning and hippocampal atrophy in the early detection of AD. But first and foremost, and by distinguishing MCI-CB but not MCI-S from HCS, our results support the value of early subcortical shape alterations and reduced hippocampal subfield volumes as potential markers for the early detection of AD.

5.3.2 Introduction

Alzheimer's disease (AD) is a neurodegenerative brain disorder characterized by progressive dementia, with current treatments providing only temporary symptomatic stabilisation. Improved treatment methods that are currently under investigation may be most efficacious in preclinical or early disease stages (Golde et al., 2011; Sperling, Jack, et al., 2011), referred to as mild cognitive impairment (MCI). In particular, subjects of the amnestic MCI subtype (aMCI) are more likely to progress to AD than subjects of the non-amnestic subtype (Roberts et al., 2014). However, the development of cognitive and clinical symptoms varies even among aMCI. Some subjects develop dementia other than AD, whereas others remain stable for a long time or even recover (Roberts et al., 2014). Thus, the establishment and validation of biomarkers that accurately identify future converters to AD is crucial.

Structural magnetic resonance imaging (MRI) represents a key imaging marker for the early detection of AD. It allows the quantification of brain atrophy due to early involvement of neurofibrillary tangle formation followed by neuronal loss. Specifically, reduced gray matter volume in medial temporal lobe regions including the hippocampal formation may precede clinical onset of AD by ten years (Tondelli et al., 2012). Consequently, the applicability of hippocampal subfield segmentation in clinical populations has gained increasing attention, with different studies providing evidence for predominant cornu ammonis (CA) 1 and subiculum atrophy in MCI (Apostolova, Dutton, Dinov, & et al., 2006; Atienza et al., 2011; La Joie et al., 2013; Pluta et al., 2012; Yushkevich et al., 2014) and AD (Apostolova, Dinov, et al., 2006; Frankó et al., 2013; Frisoni et al., 2008; Mueller et al., 2010; Mueller & Weiner, 2009; Wisse, Biessels, Heringa, et al., 2014). Although the number of studies investigating hippocampal subfields in future converters is limited, results obtained by applying surface-based subfield mapping techniques have shown similar atrophy patterns already in healthy control subjects (HCS) who later developed MCI (Apostolova et al., 2010), and in MCI who later developed AD (Apostolova, Dutton, et al., 2006; Frankó et al., 2013). Given these few findings, it is crucial to gain more information about volumetric changes of hippocampal subfields in individuals at high risk for conversion to AD.

Cortical thinning constitutes another widely accepted approach to measure gray matter atrophy in AD (Lerch & Evans, 2005). Different fully automated approaches with varying degrees of precision in terms of cortical thickness definition have been developed (e.g. MacDonald et al., 2000). Irrespective of the definition, however, cortical thinning has been found in patients with MCI and AD (Lerch, Pruessner, et al., 2008; Liao et al., 2014), in late versus early aMCI (Ye et al., 2014), and in future converters (Bakkour et al., 2009; Julkunen et al., 2010; Li et al., 2012; Liao et al., 2014).

Despite evidence for subcortical amyloid and neurofibrillary tangle formation (Braak & Braak, 1990, 1991b), MRI research has drawn its attention to subcortical structure changes only recently. Advanced segmentation techniques now permit the quantification of subcortical volumes and provide the basis for subcortical shape analyses. Although volume loss and/or shape alterations in the thalamus (Roh et al., 2011; Stepan-Buksakowska et al., 2014; Zarei et al., 2010), putamen (Cho et al., 2014; de Jong et al., 2014; Roh et al., 2011) and caudate nucleus (Cho et al., 2014; Madsen et al., 2010; Roh et al., 2011) have been identified in AD, only little is known about subcortical volumetric and shape differences in MCI in

general, and in future converters in particular. Recent results of amyloid-associated subcortical alterations already in cognitively normal elderly (Schreiner et al., 2014) further emphasize the relevance of these structures in AD. Given their connection to other AD-relevant structures such as the hippocampus (Zarei et al., 2010), the thalamus and striatum in particular represent subcortical structures of interest for being investigated in early AD.

Here, we investigated morphometric alterations in MCI with stable cognitive abilities, in MCI with future conversion to AD at baseline and at time of conversion. The multi-atlas based method used for the segmentation (hippocampus and subfields; thalamus and subnuclei; striatum) has previously evidenced improved segmentation when tested against model-based segmentation procedures (Chakravarty et al., 2013). Shape changes in the thalamus and the striatum were investigated by using an extension of a previously proposed (Lerch, Carroll, et al., 2008) and recently established (Leh et al., 2014; Magon et al., 2014; Raznahan et al., 2014; Shaw, Sharp, et al., 2014) surface-based methodology. Cortical thickness was assessed by applying a fully automated algorithm using a highly precise cortical thickness definition (Lerch & Evans, 2005). Based on these advanced techniques, we aimed to gain information about the potential value of morphometric measures to improve the identification of future converters to AD.

Confirming ongoing AD related neurodegenerative processes, morphometric alterations were expected to occur in future converters at baseline with more pronounced alterations at time of conversion. In contrast, stable MCI subjects were expected to show only minimal or no alterations at all. Specifically, the pattern of AD-related neurofibrillary tangle formation indicates early pathology in anterior thalamic regions as well as hippocampal subfield CA1 followed by the subiculum and later involvement of CA2 and CA3 (Braak & Braak, 1990, 1991a, 1991b). Accordingly, we expected volume reductions in the hippocampus, thalamus and striatum, as well as in particular hippocampal (CA1, subiculum) and thalamic (anterior) subregions. Further confirming AD-related neurodegenerative patterns and the literature (Liao et al., 2014), we expected cortical thinning in mediotemporal as well as lateral cortical regions in future converters at baseline and at time of conversion. Most importantly, we assumed thalamic and striatal shape alterations to occur in both groups as well. The neuronal basis of shape alterations is yet unknown. However, subcortical volume reductions as well as possible secondary downstream effects may lead to thalamic and striatal shape alterations.

5.3.3 Methods

Participants

We selected participants from pre-existing longitudinal cohorts at the Memory Clinic of the Division of Psychiatry Research and Psychogeriatric Medicine, University of Zurich. MCI was diagnosed according to Winblad et al. (2004). Conversion to dementia was diagnosed when subjects met National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD (McKhann et al., 1984). All diagnoses were made by a multidisciplinary team under the supervision of an experienced psychiatrist.

For the present study, inclusion criteria for MCI subjects were: aMCI diagnosis and availability of MRI data at baseline and follow-up. Exclusion criteria were: left-handedness, significant medication or drug abuse as well as clinically significant neurological and psychiatric or internal disease that may affect cognition, MRI exclusion criteria, MRI findings of infarction or other focal lesions, multiple lacunes or lacunes in critical memory structures.

A total of 41 baselines from subjects with aMCI were considered for the present study. Eight subjects were excluded from the analyses due to left-handedness (n=5), structural abnormalities in the brain (n=1), and T1 parameters that were inconsistent with the MRI study protocol (n=2). The remaining population was stratified into subjects with stable cognitive abilities during an approximately 2-year follow-up (MCI-S, n=23), and subjects with future cognitive worsening and conversion to probable AD (converter at baseline MCI-CB, n=10) during an approximately 2-year follow-up. Additionally, data from the MCI-CB group at time of conversion was obtained (MCI-CC, n=10). Inclusion criteria for HCS were: stable cognitive health ascertained by clinical work up and neuropsychological testing during an approximately 2-year follow-up. Exclusion criteria were: left-handedness, evidence for abuse of alcohol and drugs, psychiatric, neurological or significant other system diseases. Three groups of HCS were identified for group wise age and gender matching with MCI-S, MCI-CB, and MCI-CC. The final demographic details are presented in Table 5. This study was approved by the cantonal ethics committee of canton Zurich, Switzerland, in accordance with the Helsinki Declaration. All participants provided written informed consent prior to study inclusion.

Magnetic resonance image acquisition

All scans were performed on the same 1.5 Tesla Phillips Achieva scanner using an 8-element head coil. Whole-brain high-resolution three-dimensional (3D) T_1-weighted structural data was obtained by using the following scanning parameters: 166 slices, repetition time: 6.9 milliseconds, echo time: 3.2 milliseconds, flip angle: 8°, field of view: 240 x 240 x 166 millimeters (anterior-posterior, foot-head, right-left), slice thickness: 1 millimeter, total scan time: 15 min.

Image processing: subcortical structures and hippocampus

Segmentation of the striatum, thalamus and its subnuclei was performed by using a newly developed label-fusion-based segmentation method that has previously proved its high accuracy (Chakravarty et al., 2013; Leh et al., 2014). Briefly, the MAGeT-Brain algorithm applies multiple automatically generated templates from a single atlas derived from manually segmented serial histological data (Chakravarty et al., 2006) comprising 108 basal ganglia and thalamic structures as defined using three different references (Gloor, 1997; Hirai & Jones, 1989; Schaltenbrand & Wahren, 1977). We used two of the segmentations produced from the MAGeT-Brain pipeline, the first are the whole striatum (caudate and putamen) and thalamus, and the second are the thalamic subnuclei as per the Hirai and Jones (1989) definitions. The thalamus was segmented into pulvinar-, anterior-, and central nuclei and lateral dorsal-, lateral posterior-, medial dorsal nuclei, ventral anterior (VA)-, ventral lateral (VL)-, ventral posterior (VP) nuclei and lateral geniculate nucleus (LGN) and medial geniculate nucleus (MGN) as per the Hirai and Jones (1989) nomenclature. Segmentation of the hippocampus and its subfields was performed using five high-resolution atlases developed and validated for use with MAGeT-Brain (Pipitone et al., 2014; Winterburn et al., 2013). The hippocampus was segmented into CA1, CA2-CA3, CA4/Dentate gyrus, strata radiatum/lacunosum/moleculare, and subiculum.

Furthermore, total incranial volume (eTIV) was estimated following a previously validated procedure (Buckner et al., 2004).

Surface-based shape analyses

Striatal and thalamic shape analysis was performed by using an adapted surface-based methodology (Leh et al., 2014; Lerch, Carroll, et al., 2008; Magon et al., 2014; Raznahan et al., 2014; Shaw, Sharp, et al., 2014). Briefly, surface-based representations of the striatum and thalamus were defined on the input atlas. The nonlinear portions of the transformations that map each subject to the input template were concatenated and then averaged to limit the effects of noise and error and to increase precision and accuracy. Next, the dot product between the nonlinear deformation vector (of the inverse of the averaged atlas-to-subject transformation) and the surface normal at each vertex (a unit vector describing the direction perpendicular to the surface) was estimated. This measure provides an estimate of the local measure of inward or outward displacement along the normal. Resulting inward and outward displacements (measured in millimeters) were estimated relative to a detailed subcortical atlas previously described (Chakravarty et al., 2006). An inward displacement (contraction) represents a surface that is deformed inwards relative to the model that we were using and vice-versa for the outward displacement (expansion).

Cortical thickness analyses

Cortical thickness was estimated by using the automated CIVET pipeline (version 1.1.10; Montreal Neurological Institute at McGill University, Montreal, Quebec, Canada) (Ad-Dab'bagh et al., 2006). Briefly, the native images were linearly registered to the symmetric ICBM 152 template (Collins et al.,

1994; Mazziotta et al., 2001). Intensity non-uniformities were corrected using the N3 algorithm (Sled et al., 1998). The skull was removed (Smith, 2002), and brain tissue was segmented into white matter, gray matter, cerebrospinal fluid (CSF) using the Intensity- Normalized Stereotaxic Environment for Classification of Tissues (INSECT) algorithm (Tohka et al., 2004; Zijdenbos et al., 1998). Deformable models were used to construct the inner white matter surface and gray matter-CSF interface in both hemispheres (Kim et al., 2005) revealing 40,962 vertex points at each surface. Cortical thickness was then measured as the distance, in millimeters, between each vertex point at the inner and the corresponding point at the outer surface using the method proposed by Lerch and Evans (2005). The cortical thickness maps were blurred using a 20mm diffusion smoothing kernel (Chung & Taylor, 2004) to increase signal-to-noise ratio and statistical power.

Statistical analyses

Group comparisons of demographic data were applied using analysis of variance (ANOVA) or Mann-Whitney U Test. Pearson's chi-square test was used for categorical variables. Between-group differences in volumetric raw data (MCI-S, MCI-CB and MCI-CC versus matched HCS) were examined by including age and gender as covariates in the multiple linear regression models. These analyses were repeated by using volumes relative to eTIV (volume/eTIV * 100) in order to adjust volumes for differences in head size. *P* values resulting from volume analyses were adjusted for multiple testing by using Bonferroni Holms correction. Tests were performed with a significance level of $p<0.05$. The same models were performed for investigating between-group shape and cortical thickness differences. Vertex-wise analyses results are reported on a *q*-value corrected for multiple testing, using a false discovery rate (FDR) rate of 10% as in previous publications in our group (Janes, Park, Farmer, & Chakravarty, 2014). Statistical analyses were performed with IBM SPSS statistics 21 and RMINC package (R for Medical Imaging NetCDF; https://github.com/Mouse-Imaging-Centre/RMINC), an image analysis software library developed for the R statistical environment (http://www.r-project.org).

5.3.4 Results

Demographics

Descriptive statistics for demographic information is listed in Table 5. There were no significant differences in terms of age, education and gender between patient groups and controls. However, all patient groups showed significantly lower MMSE scores than their controls (Group 1 U=100.5, p=.000; Group 2 U=7.500, p=.000; Group 3 U=.500, p=.000).

Volumetric analyses in MCI-S

Apart from reduced bilateral striatal volumes (left t=2.59, p=.013; right t=2.91, p=.006, df=3,42), and when analyzing volumes relative to eTIV, there were no volume differences in any of the investigated structures in MCI-S (Table 6). Significance and p-values were similar when using raw volumes instead of volumes relative to eTIV (Supplementary Table 1). A segmentation map of the thalamus is shown in Figure 3, and of the hippocampus in Figure 4.

Volumetric analyses in MCI-CB

In contrast, pronounced reductions in volumes relative to eTIV were found in MCI-CB (see Table 6). In particular, and apart from CA2-CA3 volumes, all bilateral hippocampal subfield volumes were smaller in MCI-CB compared to HCS (right CA1 t=3.23, p=.005; subiculum t=3.29, p=.005; CA4/Dentate gyrus t=3.80, p=.002; strata t=4.55, p=.000 / left CA1 t=5.18, p=.000; subiculum t=4.96, p=.000; CA4/Dentate gyrus t=4.66, p=.000; strata t=5.91, p=.000; df=3,16) (Figure 5). With regard to thalamic subnuclei, and although statistically significant, effects of volume reductions in bilateral VP in MCI-CB (right p=.047, left p=.015) did not survive the correction for multiple testing. Significance and p-values were similar when using raw volumes instead of volumes relative to eTIV. However, some of the right hemispheric differences in hippocampal subfield volumes did not quite achieve the level of significance (CA1 p=.057). Additionally, and although statistically significant, two right hemispheric effects did not survive the correction for multiple comparisons (CA4/Dentate gyrus p=.017; subiculum p=.027) (Supplementary Table 1).

Volumetric analyses in MCI-CC

Further extended reductions in volumes relative to eTIV occurred in MCI-CC (see Table 6). More precisely, all bilateral hippocampal subfield volumes were smaller in MCI-CC compared to HCS (left CA1 t=5.09, p=.000; subiculum t=5.00, p=.000; CA2-CA3 t=4.01, p=.001; CA4/Dentate gyrus t=6.66, p=.000; strata t=9.41, p=.000 / right CA1 t=3.24, p=.005; subiculum t=3.91, p=.001; CA2-CA3 t=2.18, p=.044; CA4/Dentate gyrus t=4.47, p=.000; strata t=5.53, p=.000; df=3,16) (Figure 5). Similar as in MCI-CB, effects of VP volume reductions in MCI-CC (right p=.054, left p=.009) did not survive the correction for multiple testing. Significance and p-values were similar when using raw volumes instead of volumes

relative to eTIV. However, two right hemispheric effects in hippocampal subfield volumes did not quite achieve the level of significance (CA1 *p*=.074; CA2-CA3 *p*=.057) (Supplementary Table 1).

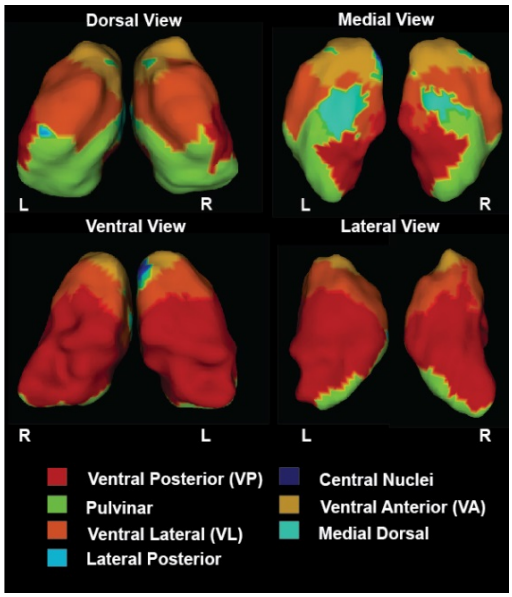

Figure 3 Automated segmentation of thalamic subnuclei. Surface labels for thalamic subnuclei, based on expert neuroanatomical labeling of serial histology (Chakravarty et al., 2006). Figure reproduced with kind permission of Leh et al. (2014).

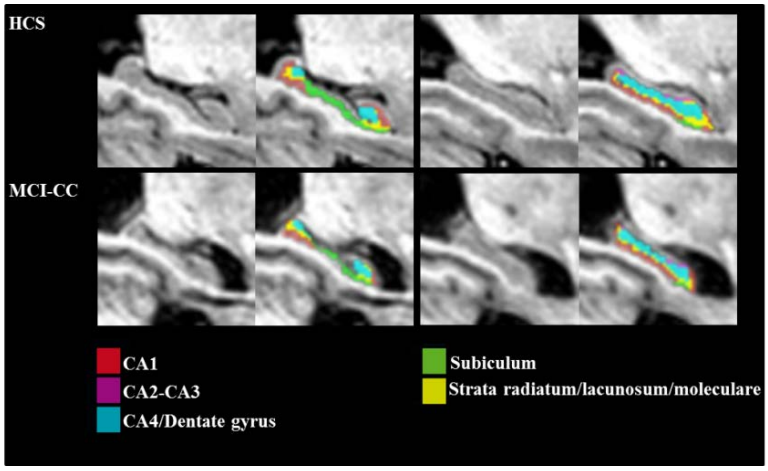

Figure 4 Automated segmentation of hippocampal subfields. CA = cornu ammonis. Coronal views of the hippocampus and hippocampal subfields in magnetic resonance images from a healthy control subject (HCS) and a mild cognitive impairment converter at time of conversion (MCI-CC).

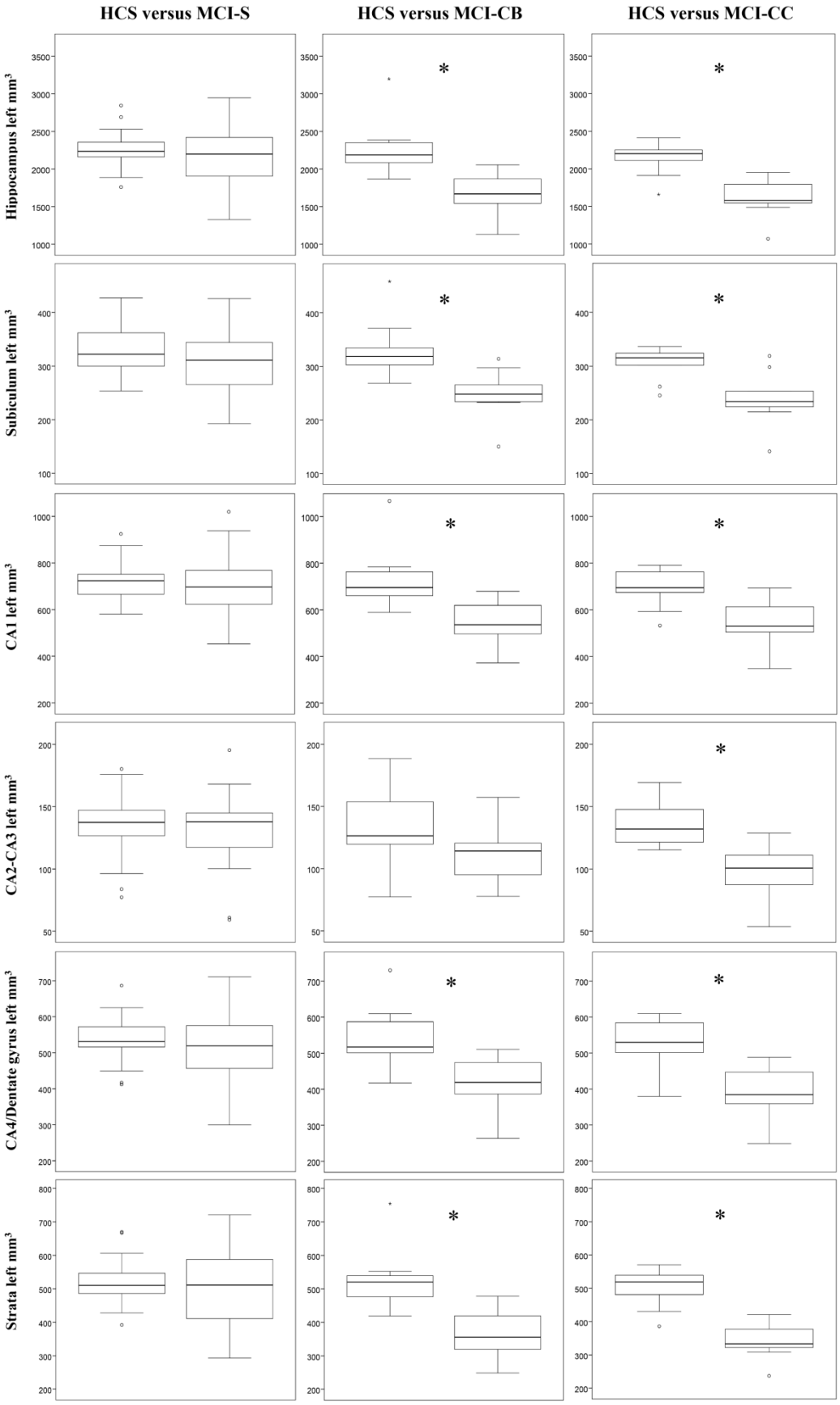
HCS versus MCI-S
HCS versus MCI-CB
HCS versus MCI-CC
Hippocampus left mm³
Subiculum left mm³
CA1 left mm³
CA2-CA3 left mm³
CA4/Dentate gyrus left mm³
Strata left mm³
*

Figure 5 Reduced left hippocampal total and subfield volumes in future converters at baseline and at time of conversion. Subjects with stable mild cognitive impairment (MCI-S) exhibited similar hippocampal total and subfield volumes whereas future converters at baseline (MCI-CB) showed reduced hippocampal volume and reduced volumes in all but one (cornu ammonis [CA]2-CA3) hippocampal subfields when compared with healthy control subjects (HCS). Correspondingly, converters at time of conversion (MCI-CC) showed reduced hippocampal volume and reduced volumes in all hippocampal subfields. Data is only shown for the left hemisphere. Results are similar for the right hemisphere though. * $p \leq .001$ significant *p* value test by using volumes relative to eTIV as dependent variable, and including age and gender in the model. Results were corrected for multiple testing and were similar when analyses were performed by using raw volumes as dependent variable. However, some of the right hemispheric differences in hippocampal subfield volumes did not quite achieve the level of significance in MCI-CB versus HCS (CA1 right *p*=.057) and in MCI-CC versus HCS (CA1 right *p*=.074; CA2-CA3 right *p*=.057). Additionally, and although statistically significant, two effects did not survive the correction for multiple comparisons in MCI-CB versus HCS (CA4/Dentate gyrus right *p*=.017; subiculum right *p*=.027).

Table 5 Demographic data for patient and control groups

	Group 1			Group 2			Group 3		
	HCS	MCI-S	*p*	HCS	MCI-CB	*p*	HCS	MCI-CC	*p*
N	23	23		10	10		10	10	
Age, years	70.96 5.78	71.22 6.54	.887	75.90 5.99	76.20 6.25	.914	77.40 5.34	78.00 6.24	.778
Education, years	14.35 2.69	14.17 3.01	.672	14.70 4.03	13.40 3.40	.376	13.30 2.41	13.40 3.41	.804
Gender, M/F	12/11	12/11	1.000	2/8	1/9	1.000	3/7	1/9	.582
MMSE, /30	29.83 0.38	28.09 1.67	.000*	29.30 0.95	26.60 1.95	.000*	29.30 1.06	23.50 2.55	.000*
Follow-up time, months[a]	46.91 33.89	25.91 8.41	N/A	39.50 32.35	20.80 4.98	N/A	48.10 33.22	N/A	N/A

Note. HCS = healthy control subjects; MCI-S = stable mild cognitive impairment at baseline; MCI-CB = mild cognitive impairment converter at baseline; MCI-CC = mild cognitive converter at time of conversion; MMSE = Mini Mental State Examination; N/A = not applicable. Values are means and standard deviations if not specified otherwise. * Significant *p* value test by ANOVA (normally distributed data), Mann U Whitney (not normally distributed data), and Pearson's X^2 test (categorical variables). [a] Follow-up times were calculated as follows: the time from baseline MRI to the time of conversion for MCI-CB, the time from baseline MRI to the last available visit for MCI-S, and the time from the first HCS diagnosis to the last available visit for HCS.

Table 6 Raw volumes relative to eTIV for patient and control groups

	Group 1			Group 2			Group 3		
	HCS	MCI-S	*p*	HCS	MCI-CB	*p*	HCS	MCI-CC	*p*
eTIV, cm^3	1586.33 177.35	1546.71 155.10	.424	1499.99 155.00	1498.05 133.58	.976	1487.72 132.59	1507.66 133.52	.741
Hippocampus total, left	.14206 .01670	.13915 .02510	.670	.14995 .01635	.11236 .013455	.000*	.14493 .00780	.10656 .01278	.000*
Subiculum	.02103 .00250	.01972 .00379	.162	.02210 .00243	.01650 .00230	.000*	.02060 .00222	.01579 .00260	.000*
CA1	.04545 .00509	.04568 .00773	.872	.04834 .00525	.03648 .00436	.000*	.04651 .00348	.03587 .00509	.000*
CA2-CA3	.00851 .00180	.00849 .00200	.966	.00882 .00184	.00752 .00154	.088	.00904 .00088	.00659 .00162	.001*
CA4/Dentate gyrus	.03399 .00460	.03264 .00611	.415	.03594 .00464	.02756 .00380	.000*	.03500 .00282	.02583 .00354	.000*
Strata	.03308 .00449	.03262 .00682	.821	.03475 .00417	.02428 .00335	.000*	.03377 .00247	.02249 .00255	.000*
Hippocampus total, right	.14140 .01557	.14454 .01796	.495	.14991 .01238	.12429 .02027	.001*	.14467 .00825	.11796 .01651	.000*
Subiculum	.01936 .00235	.01907 .00326	.753	.02079 .00254	.01677 .00321	.005*	.01998 .00258	.01590 .00277	.001*
CA1	.04698 .00538	.04862 .00607	.335	.05002 .00413	.04260 .00668	.005*	.04862 .00335	.04165 .00626	.005*
CA2-CA3	.00926 .00125	.00958 .00162	.449	.00961 .00135	.00848 .00195	.068	.00933 .00179	.00750 .00210	.044*
CA4/Dentate gyrus	.03396 .00414	.03464 .00396	.519	.03560 .00418	.02973 .00471	.002*	.03426 .00261	.02795 .00360	.000*
Strata	.03184 .00438	.03263 .00516	.534	.03377 .00266	.02671 .00517	.000*	.03249 .00237	.02497 .00398	.000*
Thalamus total, left	.32430 .02209	.32525 .02228	.882	.33248 .01846	.32428 .02484	.433	.32998 .02614	.31843 .02588	.431
LGN	.00705 .00084	.00701 .00066	.894	.00727 .00159	.00688 .00119	.475	.00713 .00085	.00658 .00115	.220
MGN	.01009 .00150	.10103 .00082	.898	.01017 .00133	.00965 .00126	.320	.01081 .00133	.00981 .00114	.106
Anterior nuclei	.00548 .00092	.00539. 00086	.665	.00531 .00057	.00555 .00087	.328	.00533 .00072	.00575 .00100	.257
Central nuclei	.01578 .00014	.01538 .00151	.447	.01597 .00137	.01500 .00143	.158	.01624 .00188	.01491 .00165	.177
Lateral dorsal nuclei	.00276 .00073	.00295 .00080	.418	.00283 .00074	.00324 .00054	.086	.00307 .00072	.00332 .00069	.252
Lateral posterior nuclei	.02229 .00299	.02363 .00275	.128	.02276 .00238	.02432 .00167	.108	.02363 .00197	.02401 .00233	.695
Medial dorsal nuclei	.05222 .00562	.05085 .00544	.415	.05292 .00427	.05046 .00626	.336	.05276 .00650	.04920 .00605	.290
Pulvinar	.07683 .00768	.07732 .00654	.798	.07540 .00570	.07350 .00848	.565	.07474 .00625	.07162 .00742	.556
VA	.03156 .00297	.03175 .00404	.868	.03288 .00229	.03343 .00302	.550	.03199 .00340	.03234 .00350	.979
VP	.02520 .00265	.02484 .00230	.631	.02593 .00264	.02329 .00244	.015	.02547 .00208	.02202 .00264	.009
VL	.04554 .00444	.04591 .00551	.810	.04858 .00363	.04578 .00585	.156	.04691 .00351	.04434 .00674	.268
Thalamus total, right	.32413 .02336	.32019 .02076	.567	.33124 .01278	.31827 .02027	.083	.32838 .02470	.31547 .02189	.257
LGN	.01136 .00138	.01143 .00134	.861	.01190 .00125	.01203.002108	.947	.01177 .00096	.01160 .00211	.626

MGN	.01235 .00142	.01226 .00109	.790	.01268 .00096	.01262 .00148	.875	.01314 .00120	.01264 .00181	.581
Anterior nuclei	.00759 .00109	.00720 .00146	.283	.00749 .00070	.00792 .00068	.209	.00787 .00099	.00796 .00055	.912
Central nuclei	.00979 .00084	.00948 .00078	.218	.01003 .00060	.00968 .00075	.237	.01021 .00117	.00960 .00073	.224
Lateral dorsal nuclei	.00309 .00089	.00296 .00077	.570	.00299 .00058	.00329.00064	.180	.00302 .00063	.00334 .00060	.084
Lateral posterior nuclei	.01683 .00247	.01672 .00216	.886	.01594 .00158	.01687 .00132	.213	.01708 .00147	.01680 .00124	.988
Medial dorsal nuclei	.04785 .00373	.04630 .00452	.226	.04823 .00430	.04647 .00435	.370	.04928 .00685	.04610 .00474	.222
Pulvinar	.09388 .00827	.09504 .00743	.569	.09443 .00553	.08914 .00799	.114	.09228 .00659	.08769 .00847	.307
VA	.03362 .00285	.03242 .00400	.246	.03532 .00326	.03405 .00280	.261	.03404 .00323	.03352 .00297	.509
VP	.03795 .00441	.02331 .00260	.753	.02382 .00180	.02196 .00257	.047	.02337 .00163	.02135 .00253	.054
VL	.03876 .00349	.03715 .00435	.221	.04071 .00302	.03818 .00468	.109	.03925 .00388	.03786 .00485	.339
Striatum total, left	.51914 .03450	.49659 .02327	.013*	.51636 .03540	.50261 .03202	.482	.49783 .02986	.50050 .03693	.936
Striatum total, right	.51211 .03543	.48445 .02920	.006*	.50521 .03297	.49679 .02506	.557	.49142 .02774	.49558 .02767	.917

Note. HCS = healthy control subjects; MCI-S = stable mild cognitive impairment at baseline; MCI-CB = mild cognitive impairment converter at baseline; MCI-CC = mild cognitive converter at time of conversion; eTIV = estimated total intracranial volume; CA = cornu ammonis; LGN = lateral geniculate nucleus; MGN = medial geniculate nucleus; VA = ventral anterior nuclei; VP = ventral posterior nuclei; VL = ventral lateral nuclei. Values represent means and standard deviations of raw volumes relative to eTIV and multiplied by 100 (volume/eTIV * 100). * Significant *p* value test by using volume/eTIV * 100 as dependent variable, and including age and gender in the model, and after correction for multiple testing.

Vertex-wise cortical thickness analyses in MCI groups

Analyses on data corrected for multiple testing by using FDR at q<.10 revealed no cortical thinning in MCI-S compared to HCS. Reduced cortical thickness, however, was found in MCI-CB and MCI-CC (Figure 6, Table 7). Significant effects were limited to medial parts such as the left parahippocampal cortex, left subgenual cingulate, and left region of the uncus in MCI-CB. Similar regions showed cortical thinning in the right hemisphere, with significance only at q<.15 though (Figure 6). Importantly, the pattern of cortical thinning extended to the right hemisphere in MCI-CC, where cortical thinning in bilateral parahippocampal cortices and bilateral regions of the uncus now achieved an appropriate level of significance.

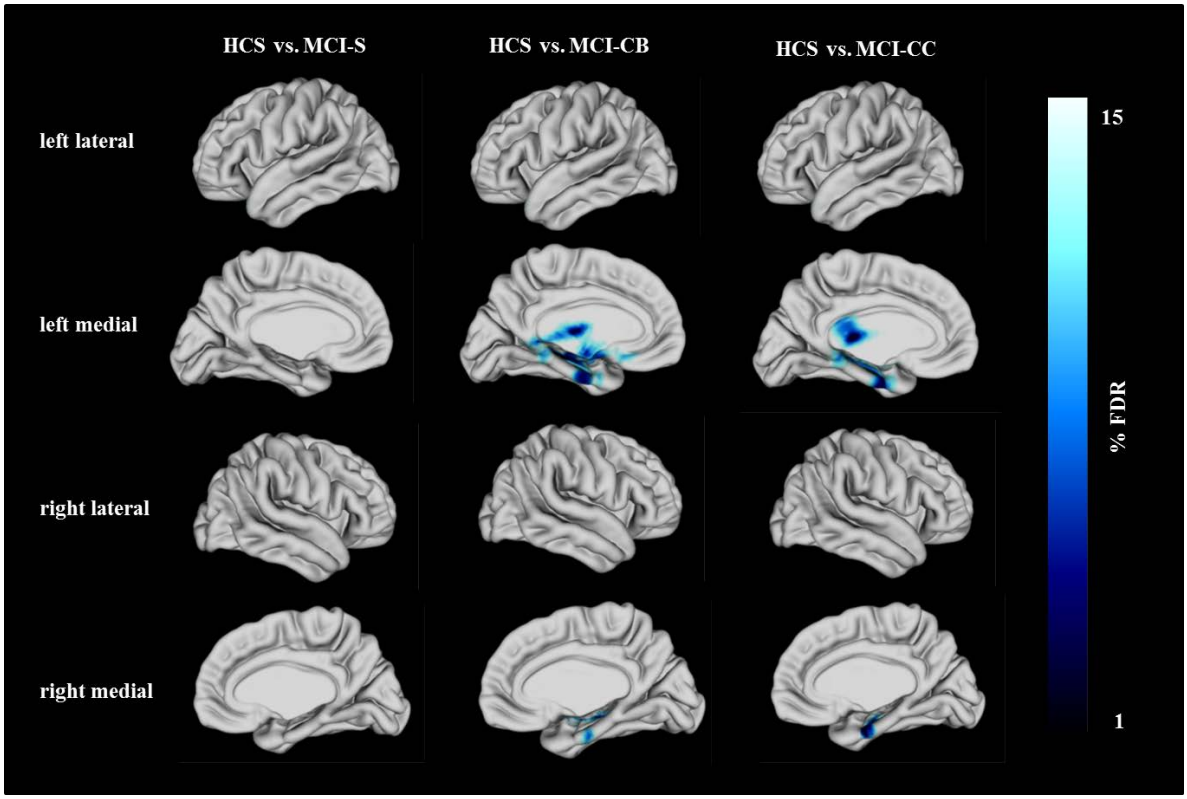

Figure 6 Reduced cortical thickness in future converters at baseline (MCI-CB) and at time of conversion (MCI-CC) but not in subjects with stable cognitive abilities (MCI-S) when compared with healthy control subjects (HCS). Images were generated after including age and gender in the model, and after correction using the False Discovery Rate (FDR) at q=.15 to better illustrate the anatomical localization. Bar shows the FDR-values, with blue – light blue indicating reduced cortical thickness.

Table 7 Reduced cortical thickness in patients groups

A

Anatomic localization	MNI coordinates (peak)			*t* statistic (peak)
	x	y	z	
Parahippocampal Cortex, left	-30	-16	-27	-5.77**
Subgenual Cingulate, left	-18	15	-14	-4.34**
Uncus, left	-29	-29	-8	-6.53**

B

Anatomic localization	MNI coordinates (peak)			*t* statistic (peak)
	x	y	z	
Parahippocampal Cortex, left	-25	-13	-32	-7.13**
Uncus, left	-31	-12	-23	-7.06**
Parahippocampal Cortex, right	29	-12	-28	-5.45*
Uncus, right	31	-10	-22	-5.20*

Note. Anatomical localization of cortical thinning in mild cognitive impairment converter at baseline (**A**), and in mild cognitive impairment converters at time of conversion (**B**). * significant after including age and gender in the model, and after correction using False Discovery Rate at q<.10. ** significant after including age and gender in the model, and after correction using False Discovery Rate at q<.01.

Vertex-wise subcortical shape analyses in MCI groups

Analyses on data corrected for multiple testing by using FDR at q<.10 showed no striatal or thalamic shape alterations in MCI-S, but pronounced striatal and thalamic displacements in MCI-CB and MCI-CC compared to HCS.

Thalamic contractions and expansions are presented in Figure 7A. In contrast to MCI-S, MCI-CB and MCI-CC showed contractions which were limited to dorsal and medial parts, and were more pronounced in the left than in the right hemisphere. Specifically, MCI-CB exhibited contractions in bilateral dorsal aspects of the pulvinar, bilateral dorsal aspects of VP, and in left medial aspects of VP and medial dorsal nuclei. Again, the pattern of alterations had further continued in MCI-CC, exhibiting more pronounced contractions extending from dorsal aspects of the pulvinar and VP to dorsal aspects of VL, lateral posterior nuclei, and VA in the right hemisphere. In contrast, contractions in the left hemisphere were now limited to dorsal aspects of VL, VA, and medial dorsal nuclei. However, there was a tendency towards significant contractions (q=.15) in dorsal aspects of the pulvinar, VP and lateral posterior nuclei as well. Thalamic expansions in turn were limited to ventral and medial parts. MCI-CB showed expansions in bilateral ventral aspects of the central nuclei, VA, VL and VP. MCI-CC showed the same,

though more pronounced pattern of expansions in both hemispheres, with additional expansion in the medial aspect of the medial dorsal nuclei.

Striatal displacements are presented in Figure 7B. Again in contrast to MCI-S, the other groups displayed contractions, predominantly in the left hemisphere and most pronounced in ventral (inferior) aspects. More precisely, MCI-CB showed contractions in medial parts of the putamen and anterior parts of the striatum (caudate head). The same pattern was found in MCI-CC, with more pronounced alterations in left ventral (inferior) medial parts of the putamen and with continued spreading to the left dorsal medial striatum (caudate body) and to right ventral (inferior) aspects of the anterior striatum (caudate head). Similar to the contractions, striatal expansions were more pronounced in the left hemisphere: MCI-CB showed pronounced expansions in ventral aspects of the anterior striatum (caudate head) and lateral putamen. MCI-CC showed a similar pattern, but with further continued expansions to ventral (inferior) aspects of the left striatum (caudate tail), and to ventral aspects of the anterior striatum (caudate head) of the right hemisphere.

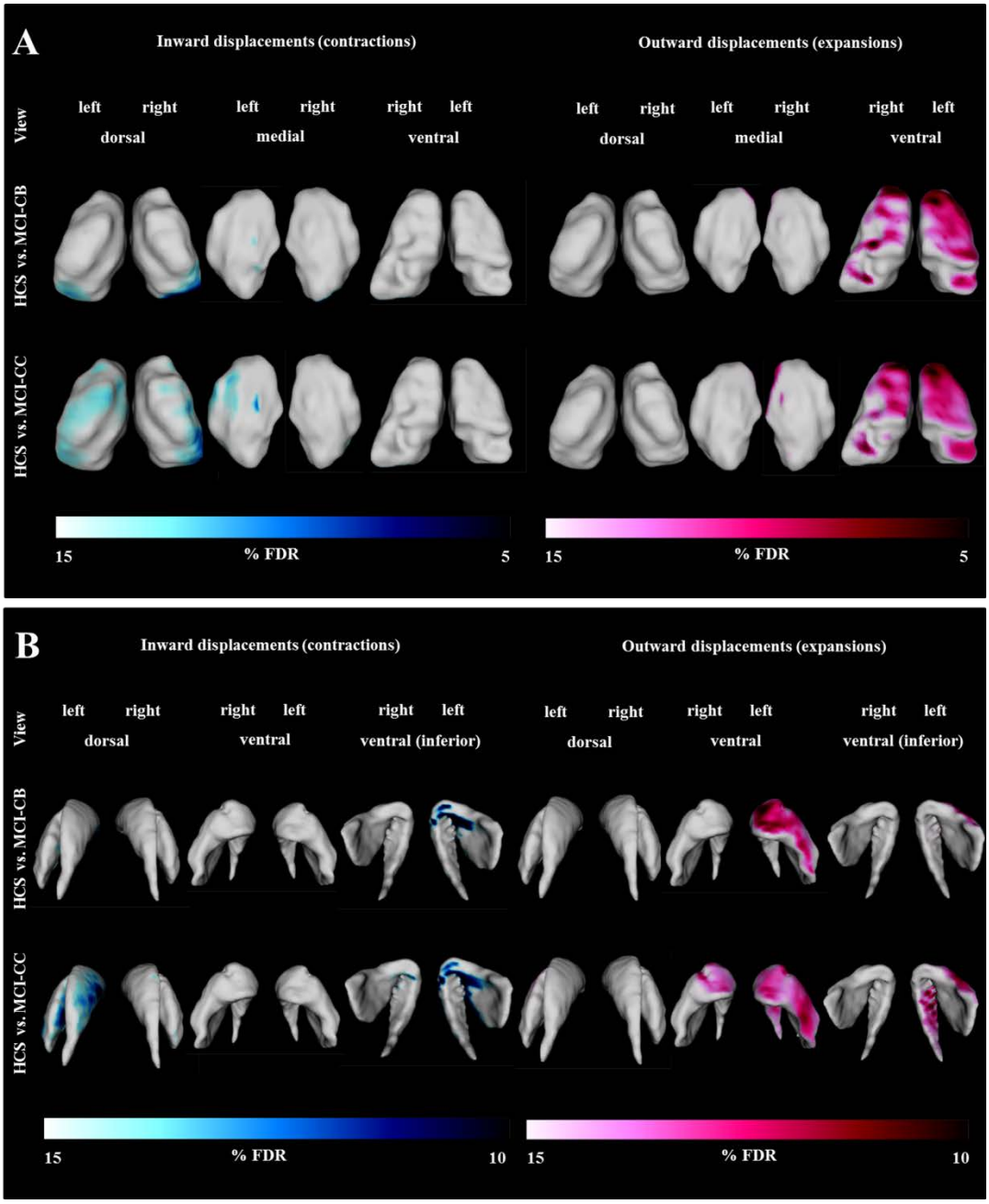

Figure 7 Regions of significant thalamic and striatal shape alterations in future converters at baseline (MCI-CB) and at time of conversion (MCI-CC) when compared with healthy control subjects (HCS). Images for differences in thalamic displacements (**A**) and striatal displacements (**B**) between groups were generated after including age and gender in the model, and after correction using the False Discovery Rate (FDR) at q=.15 to better illustrate the anatomical localization. Bars show FDR rate-values, with blue – light blue indicating inward displacements (contractions) and pink – light pink indicating outward displacements (expansions).

5.3.5 Discussion

In the current study we applied newly developed and already well-established structural imaging techniques which allowed us to characterize future converters to AD through cortical thinning, hippocampal total and subfield atrophy as well as thalamic and striatal shape alterations already at predementia stage.

Cortical thinning in future converters

Cortical thinning was not present in MCI-S compared to HCS. As expected, however, we found pronounced cortical thinning in left parahippocampal regions including the uncus in MCI-CB with further progression to bilateral regions in MCI-CC. This pattern is consistent with Braak staging (Braak & Braak, 1991b) and with memory impairment associated morphometric changes in early AD (Drago et al., 2011; Venneri, McGeown, et al., 2011).

Additionally, our results are in agreement with other studies reporting prominent thinning in parahippocampal regions in future converters (Julkunen et al., 2010; Li et al., 2012). Moreover, thinning in this region has been reported faster in future converters than in non-converters (Li et al., 2012), and being present in AD (Julkunen et al., 2010; Lebedev et al., 2013; Lerch, Pruessner, et al., 2008; Li et al., 2012). Similarly, atrophy in regions of the uncus has been identified in MCI (Venneri, McGeown, et al., 2011) and AD (Hartikainen et al., 2012; Rami et al., 2012). Like others (Lebedev et al., 2013), we also identified cortical thinning in the subgenual cingulate region in MCI-CB. Functionally, this region has been related to normal sadness reactions (Phan, Wager, Taylor, & Liberzon, 2002), and reduced volumes have been observed in patients with major depressive disorder (Drevets, Price, & Furey, 2008). Although clinically significant depression was one of the exclusion criteria in our study, very subtle but not measurable depressive symptoms in MCI-CB may have triggered this finding. The subgenual region has furthermore been associated with the uptake of serotonin (Lanzenberger et al., 2013). Serotonin is involved in the regulation of sleep (Portas, Bjorvatn, & Ursin, 2000) which is disturbed in AD (Westerberg et al., 2012).

However, our results of cortical thinning being limited to medial regions are in contrast to our expectation and the literature. Others have described more widespread, though heterogeneous patterns of cortical thinning covering not only medial but also lateral cortical regions including inferior, middle and superior temporal regions (Bakkour et al., 2009; Julkunen et al., 2010; Li et al., 2012; Liao et al., 2014), inferior and superior parietal lobe regions (Bakkour et al., 2009; Julkunen et al., 2010; Li et al., 2012; Liao et al., 2014) and inferior and superior frontal lobe areas (Dickerson et al., 2009; Julkunen et al., 2010; Li et al., 2012; Liao et al., 2014) in future converters and in AD patients. Nevertheless, also Julkunen and colleagues (2010) have documented cortical thinning in MCI-CB being limited to medial temporal regions. But in contrast to our own findings, their AD subjects have shown an extended pattern of lateral thinning. The limitation of cortical thinning to medial parts in our MCI-CC is most likely related to the fact that this group comprises the same subjects as MCI-CB at time of conversion and hence, at very early

disease stages. In contrast, AD and MCI groups consisted of different subjects in other studies (Julkunen et al., 2010; Li et al., 2012; Liao et al., 2014), with AD patients presumably representing advanced disease stages.

Hippocampal atrophy in future converters

MCI-S revealed no global or local hippocampal volume reductions compared to HCS. However, in accordance with the AD literature (Ferrarini et al., 2014; Stepan-Buksakowska et al., 2014) and our expectations, we found reduced volumes of bilateral hippocampi in MCI-CB and MCI-CC. But first and foremost, we found reduced local volumes of all but one (CA2-CA3) bilateral subfields already in MCI-CB, and of all bilateral subfields in MCI-CC.

Hippocampal shrinking represents the key imaging marker in AD research. The successful identification of hippocampal subfields by using high-field MRI, however, has offered a more local approach (Antharam et al., 2012; Mueller et al., 2010; Mueller & Weiner, 2009; Wisse, Biessels, Heringa, et al., 2014; Yushkevich et al., 2009). Advances in segmentation and analyses techniques have now enabled the field to identify hippocampal subfield alterations on images obtained from clinical standard systems. Corresponding with the pattern of neurofibrillary tangle formation, predominant CA1 atrophy has been found in MCI (Apostolova, Dinov, et al., 2006; Atienza et al., 2011; La Joie et al., 2013; Pluta et al., 2012; Yushkevich et al., 2014), with some of these studies having reported additional subicular alterations (Atienza et al., 2011; La Joie et al., 2013). A more extended pattern also including CA2 and CA3 or even CA4/Dentate gyrus has been identified in AD (Apostolova, Dinov, et al., 2006; Frankó et al., 2013; Frisoni et al., 2008; Li et al., 2013). Importantly, alterations in these subfields have been related to impaired memory functions in aMCI (Atienza et al., 2011; Ferrarini et al., 2014). Local analysis of the structure, therefore, has been suggested advantageous for the early detection of dementia (Tang et al., 2014).

Nevertheless, only a few studies have examined hippocampal subfields in future converters. Even though they have applied surface-based subfield imaging without providing volumetric information, results of alterations in CA1 and/or subiculum in future converters to MCI (Apostolova et al., 2010) or to AD (Apostolova, Dutton, et al., 2006; Chételat et al., 2008; Frankó et al., 2013) are in agreement with our own findings. In line with further progression of tangle accumulation (Braak & Braak, 1991b), we found similar bilateral CA2-CA3 volumes in MCI-CB but reduced bilateral CA2-CA3 volumes in MCI-CC compared to HCS. Additionally, we found bilateral CA4/Dentate gyrus volumes being lowered not only in MCI-CC but also in MCI-CB. Although this results contrasts the assumed spatial progression of tangle distribution in MCI-CB, similar findings have been reported by others (Pluta et al., 2012). We also identified reduced volumes of bilateral strata lacunosum/radiatum/moleculare in MCI-CB and MCI-CC, and our results are supported by studies reporting stratum radiatum and stratum lacunosum/moleculare of CA1 being affected by early tangle accumulation (Braak & Braak, 1997; Braak, Alafuzoff, Arzberger, Kretzschmar, & Del Tredici, 2006; Thal et al., 2000) and atrophy in mild AD (Kerchner et al., 2010). Method wise, it has to be noted that only a few protocols exist allowing for the reliable, automated segmentation of hippocampal subfields (see Wisse, Biessels, & Geerlings, 2014 for a critical discussion).

Here, we used a multi-atlas based segmentation approach (Chakravarty et al., 2013) that has recently evidenced high reliability and to perform equally well and probably better than other established methods (Pipitone et al., 2014).

Thalamic shape alterations in future converters

MCI-S did not reveal any deviation from HCS, neither in thalamic total or subfield volumes nor in shape alterations.

Interestingly, and against our expectation, the same was true for both, total and local thalamus volumes in MCI-CB and MCI-CC. To date, the reliable identification of thalamic subnuclei has been addressed by using diffusion tensor imaging techniques at 1.5 Tesla (Kumar, Mang, & Grodd, 2014; Lyness, Alvarez, Sereno, & MacSweeney, 2014; Zarei et al., 2010), and by applying new image processing techniques on data acquired from 1.5 up to 7 Tesla systems to visualize some of the nuclei (Abosch, Yacoub, Ugurbil, & Harel, 2010; Bender, Manz, Korn, Nagele, & Klose, 2011; Deoni, Josseau, Rutt, & Peters, 2005; Kanowski et al., 2014). Reports about detailed segmentation and quantification of thalamic subnuclei volumes in MCI and AD, however, are rare. Different studies have indeed reported reduced thalamic total volumes in MCI-CB (Bossa et al., 2011) and AD (de Jong et al., 2008; Roh et al., 2011; Stepan-Buksakowska et al., 2014; Zarei et al., 2010). Nevertheless, thalamic atrophy in AD is debated, particularly in early disease stages (Braak & Braak, 1991a; Paskavitz, Lippa, Hamos, Pulaski-Salo, & Drachman, 1995; Xuereb et al., 1991), where only a few regions are affected by a small number of isolated neurofibrillary tangles (Braak & Braak, 1991b). Hence, it is not surprising that there was only a trend toward reduced VP volumes in MCI-CB and in MCI-CC. Accordingly, our results are in agreement with other studies having observed similar volumes in aMCI (Leh et al., 2014), MCI and AD patients (Cho et al., 2014; Tang et al., 2014).

But first and foremost, and despite the absence of volumetric differences, we identified a widespread pattern of shape alterations in MCI-CB and MCI-CC. Confirming our expectation, the pronounced thalamic shape alterations in VA found in MCI-CB and MCI-CC cover regions that are affected from early neurofibrillary tangles and later occurring amyloid deposition (Braak & Braak, 1991b). Importantly, the thalamus plays a crucial role in the Papez circuit with the anterior thalamus and the pulvinar, both having shown shape alterations in MCI-CB and MCI-CC, being directly connected to the hippocampus (Zarei et al., 2010). Furthermore, frontostriatal circuits link dorsolateral prefrontal, anterior cingulate, and orbitofrontal cortex regions (Alexander, DeLong, & Strick, 1986) via the striatum and globus pallidus (Haber, 2003) to VA and medial dorsal aspects of the thalamus (Bonelli & Cummings, 2007; Tekin & Cummings, 2002), aspects that again have showed shape alterations in MCI-CB and MCI-CC. Further significant shape alterations were found in the VP, VL and lateral posterior nuclei connecting the structure with the somatosensory, motor, premotor and prefrontal and temporal and parietal cortices (Behrens et al., 2003; de Bourbon-Teles et al., 2014). Consistent with these extensive connections, thalamic regions affected from shape alterations in MCI-CB and MCI-CC have been linked with memory and frontal executive, attention, visuospatial perception, and emotion processing (Arend et al., 2014; de Bourbon-Teles et al., 2014; Saalmann, 2014; Wilke et al., 2013), with all of these functions being

impaired early in AD (Klekociuk et al., 2014). Moreover, thalamic shape alterations similar to the ones in the present study have been found to be significantly correlated with learning abilities in aMCI in a recent study from our own group (Leh et al., 2014).

To our knowledge at present, there is only one study that has investigated subcortical shape alterations in MCI-S and MCI-CB, however, without comparing their data to HCS (Tang et al., 2014). Nevertheless, the contractions found in the pulvinar and dorsal aspects of the VP in MCI-CB are consistent with contractions that have been identified in aMCI by an earlier study of our group (Leh et al., 2014). Additionally, the authors have documented contractions in regions that remained unaffected in the present MCI-CB sample such as the VL and lateral posterior nuclei. These, however, showed contractions in the MCI-CC group. Our finding of contractions in the pulvinar and dorsal as well as medial dorsal regions in MCI-CC in turn is consistent with other study results (Cho et al., 2014; Qiu, Fennema-Notestine, Dale, & Miller, 2009; Stepan-Buksakowska et al., 2014). Results about thalamic expansions in MCI and AD are few and inconsistent. In contrast to expansions in ventral regions in both MCI-CB and MCI-CC, the earlier study from our group has identified expansions in more lateral aspects in aMCI, whereas others have reported expansions in medial or even dorsal aspects in MCI and AD (Qiu et al., 2009; Tang et al., 2014). Further studies are warranted to find out whether there are typical thalamic expansion patterns for AD.

Striatal shape alterations in future converters

Surprisingly, and against our expectation, we observed reduced bilateral striatal volumes in MCI-S but similar volumes in MCI-CB and MCI-CC when compared to HCS. The most probable assumption of age- and gender-related shrinking or age-related changes in dopamine and frontostriatal networks (Abedelahi, Hasanzadeh, Hadizadeh, & Joghataie, 2013; Klostermann, Braskie, Landau, O'Neil, & Jagust, 2012) accounting for reduced striatal volumes in MCI-S renders unlikely due to age- and gender-matched HCS. Rather, the result may indicate non-AD pathology in our MCI-S sample. Normal striatal volumes in MCI-CB and MCI-CC in turn are most likely related to the early disease stages of each group. More precisely, striatal amyloid deposition and tangle formation have evidenced at late histopathological disease stages, and mainly after dementia onset (Beach et al., 2012; Braak & Braak, 1990, 1991a, 1991b; Thal et al., 2002). Hence, the striatum in MCI-CB and MCI-CC may still be free of AD-typical pathology. Correspondingly, similar volumes of the striatum, putamen and caudate in MCI and future converters compared to HCS have been reported by others (Bossa et al., 2011; Leh et al., 2014; Roh et al., 2011). Previously reported reduced volumes of the striatum, putamen and caudate in AD patients (Bossa et al., 2011; Cho et al., 2014; de Jong et al., 2014; Madsen et al., 2010; Roh et al., 2011) may in turn be related to later disease stages.

As expected, however, shape analyses revealed no alterations in the striatum in MCI-S but pronounced displacements in MCI-CB and MCI-CC. The observed shape alterations were limited to the left striatum in MCI-CB, but displacements had further spread within the structure and to the right hemisphere in MCI-CC. Aspects of the striatum showing most pronounced contractions and expansions such as the caudate head, body and tail as well as medial and lateral putamen have been linked to a wide range of cognitive

functions. More precisely, and as part of fronto-subcortical circuits, the anterior head and the body of the caudate nucleus, and the ventral lateral and medial putamen integrate major inputs from primary motor (Leh, Ptito, Chakravarty, & Strafella, 2007), dorsolateral and ventrolateral prefrontal (Leh et al., 2007), orbitofrontal, anterior cingulate (Haber, 2003) and middle temporal (de Jong et al., 2014) regions and are involved in cognitive processes such as attention, planning and memory (Cummings, 1995), all of them representing functions that are impaired early in AD (Klekociuk et al., 2014). Importantly, striatal shape alterations similar to the present ones have been associated with learning abilities in aMCI in another study from our group (Leh et al., 2014).

Again, the study from Tang et al. (2014) represents the only study we are aware of having documented shape alterations in MCI-S and MCI-CB, without comparing their data to HCS data though. In agreement with other studies, however, they have demonstrated patterns of striatal contractions in MCI and AD patients (de Jong et al., 2014; Qiu et al., 2009; Tang et al., 2014) that were comparable to the patterns found in the current study. Interestingly, only a few studies have documented striatal expansions in general (de Jong et al., 2014; Tang et al., 2014), though these expansions were less pronounced than in the present study (visual inspection).

It is beyond the aim of our study to draw direct inferences about the neuronal correlate of shape alterations. Given the pronounced connections with other disease-relevant structures, however, striatal and thalamic shape alterations may represent secondary downstream effects. A similar effect has been proposed by Stepan-Buksakowska et al. (2014). Specifically, volume reductions in the hippocampus and other early affected cortical regions may have caused subsequent morphometric changes in connected regions such as the thalamus and the striatum, without generating volume reductions yet. Although we cannot rule out the possibility of contractions representing atrophy-related alterations, the applied surface-based shape analyses provides local, but not fully comprehensive information about the entire structure. Accordingly, and as it has been shown in the present study, structural shape alterations are not necessarily associated with corresponding volume changes. Hence, our results of shape differences in the absence of volume differences highlight the importance of considering shape changes along with established volume measures.

Limitations

Relatively small subject numbers may have limited statistical power and accounted for the fact that some effects did not quite achieve the level of significance. Low standard deviations (see Table 6 and Supplementary Table 1), however, support the reliability of the present results. Furthermore, a previous study from our group has reported similar results obtained by investigating morphometric changes in MCI and HCS samples of comparable sizes (Leh et al., 2014). We are therefore confident that the current results represent stable effects. Nevertheless, further studies are required to confirm our results in larger samples.

Furthermore, the number of HCS that will convert to MCI and the number of MCI-S that will convert to AD in longer follow-up intervals is unknown, and we cannot rule out the possibility of future

conversions. This is particularly true for MCI-S subjects. Some authors have referred to this stage as potential early stage of AD (Bossa et al., 2011). Apart from slightly reduced striatal volumes, MCI-S have demonstrated no morphometric changes when compared to HCS in the present study, therefore reducing the likelihood of MCI-S representing an early disease stage. Additional markers of neurodegeneration such as CSF levels of phosphorylated Tau together with amyloid imaging may provide additional information in future longitudinal studies. The non-availability of these markers and of clinical measures providing information about disease severity in the present sample may raise the question of whether AD pathology is indeed at the basis of the observed subcortical shape alterations in the current study. The pattern of cortical thinning and hippocampal atrophy in MCI-CB and MCI-CC, together with absent morphometric alterations in MCI-S, however, are indeed highly supportive for AD pathology in MCI-CB and MCI-CC.

The similar patterns of morphometric alterations in MCI-CB and MCI-CC are most likely related to the fact that both groups consisted of the same subjects, with MCI-CC data having been obtained at time of conversion. Hence, the time lag of approximately 20.8 months between MRI at baseline and at time of conversion might have been too short to reveal further progressed morphometric alterations.

Conclusion

The simultaneous presence of thalamic and striatal shape alterations, AD-typical cortical thinning and hippocampal atrophy in MCI-CB but not in MCI-S highlights the value of subcortical shape alterations as early marker for AD, and emphasizes the importance to consider regional morphological information of subcortical structures. It is now necessary to find ways allowing the implementation of advanced segmentation and analyses techniques in everyday clinical practice in the near future.

5.3.6 Supplementary data

Supplementary Table 1 Raw volume sizes for patient and control groups

	Group 1			Group 2			Group 3		
	HCS	MCI-S	*p*	HCS	MCI-CB	*p*	HCS	MCI-CC	*p*
eTIV, cm^3	1586.33 177.35	1546.71 155.10	.424	1499.99 155.00	1498.05 133.58	.976	1487.72 132.59	1507.66 133.52	.741
Hippocampus total, left	2238.28 260.63	2150.25 434.33	.390	2250.76 374.17	1687.81 274.65	.003*	2156.61 223.12	1609.17 247.38	.000*
Subiculum	332.02 44.55	304.09 62.10	.052	331.47 51.73	248.01 43.84	.001*	305.25 29.47	238.94 48.22	.002*
CA1	716.61 83.99	706.75 141.74	.785	727.14 132.45	548.12 89.81	.004*	692.32 81.86	542.17 95.77	.004*
CA2-CA3	133.94 27.55	130.89 31.18	.729	132.45 31.93	111.93 21.82	.150	134.26 16.94	98.11 20.69	.001*
CA4/Dentate gyrus	534.68 64.87	503.78 101.15	.215	538.14 86.87	414.63 75.53	.006*	522.28 73.58	390.57 67.95	.001*
Strata	521.03 69.33	504.74 118.25	.564	521.85 93.31	365.12 67.27	.001*	502.50 56.59	339.38 50.29	.000*
Hippocampus total, right	2234.65 300.09	2232.02 340.64	.993	2244.32 274.42	1858.63 335.92	.019*	2149.88 196.89	1775.68 280.26	.006*
Subiculum	304.93 34.75	293.59 52.12	.377	311.29 45.88	251.38 54.78	.027	296.18 38.27	239.80 47.82	.009*
CA1	743.04 108.48	751.13 117.96	.782	750.52 107.06	638.02 115.92	.057	722.65 74.27	628.90 115.45	.073
CA2-CA3	146.56 23.46	147.91 27.64	.844	143.55 22.07	125.88 26.26	.119	138.63 29.32	111.37 26.32	.057
CA4/Dentate gyrus	536.26 73.05	534.87 76.72	.980	531.92 70.60	443.88 73.45	.017	509.88 61.47	420.12 57.92	.008*
Strata	503.86 85.79	504.52 95.45	.945	507.04 57.00	399.47 85.29	.007*	482.54 45.84	375.49 64.85	.001*
Thalamus total, left	5126.73 503.34	5036.59 652.23	.565	4977.11 470.58	4854.86 547.58	.886	4887.31 330.22	4792.43 195.68	.870
LGN	111.36 15.48	108.48 15.57	.522	108.08 19.89	102.21 14.05	.525	105.67 13.19	98.15 11.26	.258
MGN	159.11 24.28	156.87 22.00	.706	151.80 18.91	143.73 15.72	.404	160.02 17.57	146.96 12.99	.148
Anterior nuclei	87.56 19.90	83.39 15.61	.361	79.87 13.58	83.20 15.85	.241	78.88 9.53	86.78 18.23	.104
Central nuclei	248.49 27.52	237.58 31.05	.147	239.37 30.15	224.34 25.28	.335	240.92 30.16	223.86 23.09	.871
Lateral dorsal nuclei	44.53 14.55	45.86 13.94	.761	42.85 13.33	48.56 9.44	.083	45.40 10.29	50.02 11.52	.105
Lateral posterior nuclei	355.06 68.93	366.43 60.36	.542	341.19 47.86	364.56 43.91	.099	349.79 21.34	361.28 42.25	.331
Medial dorsal nuclei	822.66 79.53	785.62 110.11	.178	790.30 67.28	753.79 102.32	.501	779.15 65.12	738.24 83.74	.508
Pulvinar	1212.08 126.63	1195.09 146.50	.655	1128.08 113.66	1101.08 160.98	.940	1109.93 118.10	1079.69 146.41	.800
VA	500.06 67.78	493.17 89.54	.755	493.21 61.80	500.08 56.84	.367	472.95 33.09	485.61 49.05	.399
VP	396.65 33.99	383.97 50.83	.275	386.85 34.62	348.36 44.33	.050	377.78 34.68	331.26 44.02	.041
VL	719.09 80.65	711.71 117.47	.799	725.58 56.69	684.07 92.85	.283	695.61 56.70	665.58 93.58	.551
Thalamus total, right	5122.67 493.57	4958.83 643.05	.280	4959.92 448.02	4758.09 417.01	.423	4864.32 321.10	4742.79 377.55	.839
LGN	179.37 23.03	176.95 28.31	.763	177.46 14.77	178.81 25.88	.873	174.31 10.92	173.45 23.64	.928

VL	719.09 80.65	711.71 117.47	.799	725.58 56.69	684.07 92.85	.283	695.61 56.70	665.58 93.58	.551
Thalamus total, right	5122.67 493.57	4958.83 643.05	.280	4959.92 448.02	4758.09 417.01	.423	4864.32 321.10	4742.79 377.55	.839
LGN	179.37 23.03	176.95 28.31	.763	177.46 14.77	178.81 25.88	.873	174.31 10.92	173.45 23.64	.928
MGN	195.04 25.38	190.02 29.13	.439	189.86 19.72	188.17 20.73	.882	195.39 25.37	189.52 24.60	.956
Anterior nuclei	120.72 22.93	111.68 26.22	.168	112.40 16.29	119.18 18.36	.276	116.68 15.55	120.22 15.19	.468
Central nuclei	154.73 17.33	146.89 21.11	.118	150.24 16.51	144.89 16.56	.648	151.41 18.34	144.54 14.79	.625
Lateral dorsal nuclei	49.43 15.49	45.96 13.21	.374	45.14 11.29	49.85 12.83	.196	45.27 11.65	50.67 11.98	.087
Lateral posterior nuclei	267.29 47.20	259.55 47.31	.571	239.24 34.40	252.46 28.41	.234	253.76 28.45	252.63 23.74	.189
Medial dorsal nuclei	756.02 74.65	716.16 99.86	.104	720.75 68.41	693.40 61.79	.503	727.41 73.61	691.37 54.93	.385
Pulvinar	1484.26 165.02	1469.57 183.34	.749	1414.45 145.15	1331.68 137.33	.227	1370.91 138.16	1316.74 122.95	.781
VA	532.09 65.62	503.16 89.00	.204	527.86 53.61	510.49 66.36	.670	503.71 35.07	504.70 56.99	.813
VP	366.80 32.69	357.21 50.58	.402	356.18 34.07	327.49 34.56	.069	346.68 29.03	320.19 32.51	.123
VL	611.33 14.59	576.04 95.90	.156	608.29 51.25	569.12 60.62	.176	581.08 52.21	567.77 62.64	.684
Striatum total, left	8208.75 818.54	7688.01 897.51	.031*	7746.97 1003.05	7513.04 651.33	.844	7389.66 615.77	7527.29 689.44	.356
Striatum total, right	8095.68 805.24	7497.72 905.81	.015*	7575.03 917.71	7432.17 645.25	.989	7303.52 696.77	7453.16 554.69	.382

Note. HCS = healthy control subjects; MCI-S = stable mild cognitive impairment at baseline; MCI-CB = mild cognitive impairment converter at baseline; MCI-CC = mild cognitive converter at time of conversion; eTIV = estimated total intracranial volume; CA = cornu ammonis; LGN = lateral geniculate nucleus; MGN = medial geniculate nucleus; VA = ventral anterior nuclei; VP = ventral posterior nuclei; VL = ventral lateral nuclei. Values represent mean and standard deviation of raw volumes mm^3. * Significant *p* value test by using raw volumes as dependent variable, and including age and gender in the model, and after correction for multiple testing.

6 General discussion

The present work investigated whether within-domain IIV as well as thalamic and striatal shape alterations as cognitive and morphometric markers might support the identification of subjects at high risk for conversion to AD. Whereas this question could not be definitively answered with regard to the cognitive marker, the morphometric markers allowed the further characterization of future converters to AD.

6.1 Within-domain intraindividual variability as early marker

Results from study 1 investigating across- and within-domain IIV in HCS, MCI and AD have indeed provided support for within-domain IIV representing a potential early marker. Specifically, both across- and within-domain IIV were increased in AD versus HCS. However, across-domain IIV successfully discriminated between MCI and AD, whereas within-domain IIV successfully discriminated between MCI and HCS. Similar across-domain IIV in MCI and HCS as well as similar within-domain IIV in MCI and AD are most likely due to the varying levels of cognitive control functions elicited by the underlying tasks, the degree of impairment of cognitive control processes in the different groups (similar across-domain IIV in HCS and MCI), and to very subtle characteristic of accuracy-based IIV in general, and within-domain IIV in particular (similar within-domain IIV in MCI and AD). Importantly, in agreement with the literature (Tractenberg & Pietrzak, 2011), similar difference scores (across- minus within-domain IIV) across groups indicated increasing accuracy-based IIV across diagnoses in general. Positive difference scores furthermore confirmed higher across- than within-domain IIV in all groups. This result indicates that impaired cognitive control functions affect performance in different cognitive control tests to a similar extent, and lead to rather low within-domain IIV. In contrast, inconsistent performance across tests representing cognitive domains most prone to show AD-related impairment, such as episodic memory (Albert et al., 2011) and short-term memory capacity (Schmitt et al., 2009), leads to higher across-domain IIV. Additionally, IIV was higher in APOE ε4 carriers than non-carriers. This, however, was only true for within- but not across-domain IIV, and only in HCS but not in MCI or AD. The present data, therefore, provide further support for the previously suggested relationship between cognitive control functions and APOE status (Duchek et al., 2009). It may, however, be that ε4-related changes in cognitive control functions and IIV appear in HCS but may not be evident by the MCI and AD stage due to increasing impairment in other cognitive domains. Thus, based on results from study 1, it was concluded that across-domain IIV tapping less cognitive control functions may detect incipient dementia and separate AD from MCI, whereas within-domain IIV tapping cognitive control functions more closely may constitute a potential marker for the detection of prodromal AD at the MCI stage.

However, when longitudinal clinical information from MCI subjects was considered in study 2, within-domain IIV as cognitive marker for the early detection was questionable. More precisely, within-domain IIV was similar in MCI-S and MCI-CB when compared to HCS, and the same was true when MCI were

combined across groups. As suggested by the literature (Ramratan et al., 2012; Vaughan et al., 2013) and by results from study 1, accuracy-based IIV in general might still be of low characteristic utility in MCI. Thus, the rather low sample size in study 2 might not have been sufficient to compensate for the low characterization of within-domain IIV in MCI-CB, leading to similar within-domain IIV in MCI-CB and HCS. Hence, it seems as if much larger sample sizes are required to observe a stable effect when investigating accuracy-based IIV in general, and within-domain IIV in particular.

There is also the general question as to whether cognitive abilities allow the reliable identification of very early AD-relevant cognitive alterations, particularly when assessed on only one occasion. Impaired memory functions have gained attention and have been accepted as an early marker based on results from longitudinal studies clearly showing a decline up to a decade before the onset of AD (Amieva et al., 2014; Wilson et al., 2011), and being impaired already in HCS who later developed AD (Tabert et al., 2006; Venneri, Gorgoglione, et al., 2011; Wilson et al., 2012). Similar results have been shown for across-domain IIV (i.e. Holtzer et al., 2008). Despite this highly valuable, retrospectively acquired information about longitudinal development of memory functions, the identification of AD-related memory alterations at such early stages and based on memory performance obtained from one single assessment represents an entirely different situation. Specifically, it is complicated by the lack of valid and reliable tests, appropriate normative data, or cut off scores allowing for the identification of subtle cognitive deficits. For example, high educational background (Amieva et al., 2014) or individual compensational strategies might leave cognitive functions in early MCI temporarily unimpaired. In contrast, low educational background (Amieva et al., 2014), individual weaknesses, or state-based fluctuations in cognition (Kliegel & Sliwinski, 2004) might affect cognitive performance, resulting in MCI-typical cognitive profiles in cognitively normal subject. Consequently, due to this deficit-oriented approach, cognitive impairment represents the last marker becoming abnormal, and the first clinical symptom in the biomarker model proposed by Jack et al. (2013). IIV has indeed been shown to provide information about cognitive functions above and beyond mean-level performance of standardized tests (Dixon et al., 2007; Hultsch et al., 2000), and the calculation of accuracy-based IIV does not require test-specific normative data or cut off scores. Thus, the use of IIV instead of mean-level performances in AD diagnosis might offer some advantage. Nevertheless, accuracy-based IIV relies on accuracy scores obtained from established cognitive tests, and thus, might suffer from similar limitations when assessed on one occasion. As has been shown for memory scores (e.g. Amieva et al., 2014) and across-domain IIV (e.g. Holtzer et al., 2008), measures of within-domain IIV across time might be necessary to overcome some of these limitations and provide more reliable and valid information about even subtle cognitive changes on an individual basis, irrespective of cognitive impairment.

In summary, the early detection of future MCI or AD subjects solely based on test-associated cognitive markers might be restricted due to limitations that are inherent to the cognitive tests themselves. Importantly, however, cognitive measures might be of high relevance when combined with established biomarkers, as suggested by reports about improved prediction of conversion to AD when gray matter atrophy patterns (Da et al., 2014), hippocampal volumes and CSF markers (Eckerström et al., 2013) have been combined with cognitive markers.

6.2 Neuronal correlates of within-domain intraindividual variability

There has only been one study investigating neuronal correlates of accuracy-based IIV so far, indicating a relationship between accuracy-based IIV and frontal gray but not frontal white matter volumes in elderly HCS (Lövdén et al., 2013). Thus, the authors have provided further support for the relevance of frontal brain regions for IIV, and for a possible relationship between accuracy-based IIV and gray matter volumes. However, IIV has been associated with cognitive control functions, and cognitive control functions have been suggested to be supported not only by frontal (Casey et al., 2007; Levy & Wagner, 2011; Liston et al., 2006; Miller & Cohen, 2001; Weissman et al., 2006) but also by parietal cortices (Wilk et al., 2012). Considering increased within-domain IIV in MCI and AD (study 1), reduced cognitive control processes in AD (Rapp & Reischies, 2005; Schroeter et al., 2012) and AD-related cortical brain atrophy in IIV-relevant regions (e.g. Zhao et al., 2014), a relationship between within-domain IIV and frontal as well as parietal gray matter volumes was thought to be highly likely. The lack of such a relationship in the present work, however, is most likely related to the absence of frontal or parietal atrophy not only in MCI-S but also in MCI-CB. Although some studies have indeed observed prefrontal (Han et al., 2012; Mosconi et al., 2013; Zhao et al., 2014) and parietal shrinking (Clerx et al., 2013) in MCI or future converters subjects, others have failed to observe similar patterns (Burgmans et al., 2009; Zhang et al., 2013). These differences have most likely occurred due to different disease stages of MCI groups across studies. In particular, NFT in frontal and parietal regions have been identified at rather late histopathological disease stages (Braak & Braak, 1991b). Thus, MCI-CB subjects in the present work might have still been free of AD pathology. Apart from the non-existent prefrontal or parietal atrophy in MCI-CB, the low characterization of within-domain IIV might have further contributed to the lack of relationship between within-domain IIV and regional gray matter volumes.

However, the lack of such a relationship even in MCI-S and HCS contrasts with results from Lövden et al. (2013) and raises the question of whether accuracy-based IIV is indeed associated with gray matter volumes in general. So far, most of the studies exploring neuronal correlates of IIV have investigated latency-based IIV, and have provided evidence for a relationship with frontal (Bunce et al., 2007; Jackson et al., 2012; Lövdén et al., 2013; Ullen et al., 2008) as well as parietal (Bellgrove et al., 2004; Jackson et al., 2012; MacDonald, Nyberg, et al., 2008; Ullen et al., 2008; Wilk et al., 2012) white matter alterations in elderly HCS. Likewise, similar relationships have also been found in MCI and AD (Anstey et al., 2007; Jackson et al., 2012). Interestingly, some of these studies have also investigated gray matter alterations but failed to identify comparable relationships (Lövdén et al., 2013; Moy et al., 2011; Ullen et al., 2008; Walhovd & Fjell, 2007). Providing further support for a link between white matter alterations and latency-based IIV, reaction time performance in general has previously been suggested to be associated with white matter integrity (Bender & Raz, 2012; Madden et al., 2004). Moreover, results from other studies have indicated a rather generalized relationship between mean reaction time performance and gray matter alterations, and between latency-based IIV and white matter alterations (Bunce et al., 2007; Walhovd & Fjell, 2007). Generally speaking, there is increasing evidence for the relevance of white matter alterations being at the basis of IIV. Thus, a similar relationship between frontal white matter alterations and accuracy-based IIV needs to be considered. Since accuracy- and latency-based IIV have

repeatedly been found to be associated (Hilborn et al., 2009; Hultsch et al., 2002), the idea of common neuronal correlates does not seem unreasonable, and has to be investigated in elderly HCS. Given increasing evidence for white matter pathology (Gold, Johnson, Powell, & Smith, 2012; Stokin et al., 2005) and reduced white matter integrity in AD (Sun et al., 2014), such a relationship might also be at the basis of increased IIV in MCI and AD. However, the lack of a relationship between accuracy-based IIV and frontal white matter volumes in HCS in the study from Lövden et al. (2013) might indicate that white matter alterations beyond volume measurements might be necessary to shed further light on neuronal correlates of IIV in general. More precisely, since prefrontal cortex regions are involved in fronto-subcortical circuits and act within distributed networks (Dosenbach et al., 2006), the investigation of a relationship between within-domain IIV and white matter connectivity in these networks in MCI and AD might help to provide further information about neuronal correlates of IIV.

6.3 Thalamic and striatal shape alterations as early markers

Results from study 3 indicated that subcortical shape alterations might be of high value for the early detection of AD. Specifically, as expected, thalamic and striatal shape alterations occurred in MCI-CB as well as MCI-CC, whereas they were absent in MCI-S when compared with HCS. Striatal and thalamic shape changes were paralleled by AD-like patterns of hippocampal total and subfield atrophy and mediotemporal cortical thinning in MCI-CB and MCI-CC but not in MCI-S. The results therefore support the presence of AD-related atrophy in MCI-CB and MCI-CC but not in MCI-S, and indicate an association between AD pathology and shape alterations. Thus, and by taking into account the presence of cognitive impairment and neurodegeneration, MCI-CB patients in the present work revealed an intermediate likelihood for conversion to AD following most current criteria for MCI due to AD (Albert et al., 2011). In contrast, MCI-S did not meet these criteria due to the lack of neurodegeneration. Although information about Aβ deposition in the brain was not available, the diagnosis of MCI due to AD renders unlikely. Supporting previous suggestions from others (Stepan-Buksakowska et al., 2014; Tang et al., 2014), the present results further emphasize the importance of considering local structural information from different structures in order to identify an AD-typical pattern of brain alterations in early AD.

So far, many researchers have focused on measuring atrophy in medial temporal regions and comparing it between HCS, MCI and AD subjects. It has already been emphasized, however, that reduced gray matter volume sizes of single structures may not necessarily establish AD pathology (van de Pol et al., 2006). Accordingly, hippocampal atrophy has also been identified in forms of dementia other than AD (de Souza et al., 2013; La Joie et al., 2013; Lindberg et al., 2012; Tondelli et al., 2012). Hippocampal subfield analysis has indeed offered a more local approach (Wisse, Biessels, Heringa, et al., 2014), and hippocampal shape analysis has even evidenced additional predictive value over hippocampal volume for dementia in HCS (Achterberg et al., 2014). Thus, by taking into account the spreading pattern of AD pathology across the brain, the simultaneous investigation of shape and volume alterations of different structures represents a more appropriate approach to identify an AD-typical pattern of brain alterations.

Mixed results about thalamic and striatal atrophy in MCI and AD have been reported (see chapter 5 for an overview), most likely due to patient groups across studies representing different diseases stages. Nevertheless, subcortical structures such as the thalamus and the striatum in particular have been shown to be interesting and important in AD. Both structures consist of functionally different subfields which might be affected differently by AD pathology. A local approach is thus crucial. Both structures are furthermore connected with each other, and with regions that have shown early AD pathology such as the hippocampus (Zarei et al., 2010). Thus, both structures are involved in different neuronal circuits (Alexander et al., 1986; Bonelli & Cummings, 2007; Haber, 2003; Tekin & Cummings, 2002), and in different cognitive functions that are known to be impaired early in AD (Klekociuk et al., 2014). Moreover, anterior thalamic regions have revealed very early NFT pathology in AD (Braak & Braak, 1991a, 1991b). The relevance of subcortical structure changes in AD has furthermore been indicated by recent studies from our own group reporting an association between subcortical amyloid load and brain tissue alterations in elderly HCS (Fluid-attenuated inversion recovery [FLAIR]) (Schreiner et al., 2014), and amyloid-related decreased network efficiency affecting the hippocampus and thalamus in elderly HCS (functional MRI) (Steininger et al., 2014).

Only a few studies have investigated subcortical shape alterations in MCI and AD, though with promising results of shape alterations in the hippocampus, amygdala, thalamus, caudate and putamen in MCI and AD (Cho et al., 2014; de Jong et al., 2014; Stepan-Buksakowska et al., 2014; Tang et al., 2014). To the best of our knowledge at present, however, there has been only one study investigating subcortical shape alterations in future converters (Tang et al., 2014) without comparing their data to HCS though. Similar to results from studies investigating pooled MCI or AD (Cho et al., 2014; de Jong et al., 2014; Leh et al., 2014; Qiu et al., 2009; Stepan-Buksakowska et al., 2014; Tang et al., 2014), thalamic and striatal shape alterations found in the present work have been identified in regions that are involved in AD-relevant cognitive functions (see chapter 5 for an overview). Accordingly, the present results as well as the literature support a pattern of striatal shape alterations in the caudate head, body and tail as well as in medial and lateral parts of the putamen, and thalamic alterations in anterior regions, the pulvinar, as well as medial dorsal aspects of the structure. However, shape alterations have also been identified in other parts of these structures (Cho et al., 2014; de Jong et al., 2014; Leh et al., 2014; Qiu et al., 2009; Stepan-Buksakowska et al., 2014; Tang et al., 2014), indicating high variability across studies. Since thalamic and striatal shape alterations have additionally been documented in multiple sclerosis (Magon et al., 2014), attention-deficit/hyperactivity disorder (Shaw, De Rossi, et al., 2014) and obsessive-compulsive disorder (Shaw, Sharp, et al., 2014), it is crucial to identify AD-relevant deformation patterns. Further studies are therefore necessary to investigate shape alterations in MCI in general, and in future converters in particular.

Interestingly, as has been found by others (Cho et al., 2014; Tang et al., 2014), subcortical shape alterations in the present work occurred in the absence of volumetric alterations in the same structures. These results might indicate different neuronal correlates underlying shape and volumetric changes. However, there is as yet no clarity about the biological basis of contractions and expansions. Nevertheless, considering the surface-based approach applied in the present work, it must be recognized that shape analyses provide information about local deformations rather than fully comprehensive

information about the structure or its volume. Accordingly, in agreement with the present findings, structural shape changes are not necessarily accompanied by structural volume changes and vice versa. At the same time, we cannot altogether exclude the possibility of contractions representing atrophy (Cho et al., 2014), and the simultaneous presence of contractions and expansions might leave the overall volume unaffected. As discussed in the empirical part (chapter 5), however, striatal and thalamic shape changes in the present work might represent secondary downstream effects resulting from volume reductions in early affected cortical regions. Although accumulating proteins, axonal and dendritic loss, changes of synaptic structures or glial cells, or loss of cholinergic neurons may represent potential candidates, the neuronal basis of a potential secondary downstream effect, and of contractions and expansions remains unknown for the time being.

6.4 Implications and directions for future research

The present findings gave rise to new research questions. With regard to IIV, it will be fundamental to first investigate within-domain IIV longitudinally and by using much higher sample sizes to see whether stable effects of increased IIV present in future converters. Irrespective of its potential role in the early detection of AD, diffusion tensor imaging (DTI) analysis investigating the relationship between accuracy-based IIV in general and white matter connectivity within fronto-subcortical networks in elderly HCS would be of high interest, and might provide further information about the neural underpinnings of accuracy-based IIV.

With regard to subcortical shape alterations, further studies investigating thalamic and striatal shape alterations in future converters and AD are crucial to identify the typical deformation pattern that is associated with AD pathology.

Both potential markers should be investigated with regard to their association with established biomarkers such as CSF tau or PET amyloid imaging. The presence of an association with high amyloid load in elderly HCS in particular would provide support for the value of subcortical shape alterations as preclinical marker for AD. PET amyloid imaging and future tau imaging might additionally help to provide more information about neuronal correlates of shape alterations in the AD disease process.

Additionally, predictor analyses need to be performed to determine the established biomarker that deem most appropriate to improve the prediction of future conversion when combined with subcortical shape changes. Similar analyses need to be performed to find out whether within-domain IIV might contribute to the prediction of conversion when combined with more established biomarkers.

6.5 Conclusion

The present work investigated the potential value of a newly developed cognitive measure and recently developed morphometric measures as early markers for AD.

Within-domain IIV demonstrated questionable value as an early cognitive marker, and needs further exploration. In contrast, advanced imaging methods revealed that subcortical shape alterations in the thalamus and striatum, which were paralleled by AD-typical atrophy patterns in AD patients in the predementia stage, were promising for enhancing the early detection of AD.

The present work also indicates that cognitive markers in general might be of limited value for the early detection of AD when compared with morphometric alterations.

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